# TORQUOSELECTIVITY AND CHLORIDE TRAPPING IN THE NAZAROV CYCLIZATION OF FACIALLY BIASED DIENONES

by

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# ABSTRACT

A rapid method of constructing tricyclic cyclopentanones demonstrating good diastereoselectivity via the Nazarov cyclization was introduced. Torquoselectivity governed stereochemistry observed in the final products. Torquoselectivity is determined by steric interactions during the actual cyclization process. Starting with complex, readily available starting materials, complexity was increased quickly setting several stereocenters during the Nazarov cyclization.

The commercially available bicyclo[2.2.1]heptane system in camphor and bicyclo[3.1.1]heptane system of myrtenal and nopinone were used as starting materials. These facially biased systems have unique steric environments differentiating the top and bottom faces of the molecule. In three steps, each starting material was functionalized into a variety of dienones. First, each compound was converted to a hydrazone, which was submitted to Shapiro reaction conditions, generating a dienol. Oxidation of these dienols generated the desired dienones to be cyclized under Nazarov conditions.

Camphor substrates showed torquoselectivity ranging from excellent to moderate, favoring *exo*-type products. However, when $TiCl_4$ was used to cyclize these substrates, unexpected chloride incorporation occurred. Myrtenal substrates showed torquo-selectivity also, but to a lesser extent. More interestingly, the interactions present in the 3.1.1 system reverse selectivity, favoring the *endo* product. Many of these cyclizations not only displayed chloride trapping, but also Wagner-Meerwein shifts. Other titanium(IV) halogen Lewis Acids also furnished halogen trapped products.

*In loving memory of my dad.*

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# Chapter 1

# THE NAZAROV CYCLIZATION

## Introduction

One of the most challenging and important goals of organic chemistry is the total synthesis of natural products. As synthetic targets become increasingly complex, reliable and selective chemical transformations are required. Many desirable compounds contain five-membered rings with varying degrees of functionality and complexity. Formation of substituted cyclopentanoids with a high degree of selectivity is an invaluable method in the total synthesis of interesting organic molecules.

Nazarov reported a general method for the synthesis of five-membered rings in the 1940's.[1] During extensive studies on the formation of allyl vinyl ketones, Nazarov and co-workers discovered the reaction that now bears his name (Figure 1.1). When the dienyne **1** was heated with sulfuric acid and mercury (II) sulfate in aqueous methanol, a small amount of the desired allyl vinyl ketone **2** was isolated along with cyclopentenone **3**. Compound **2** was usually consumed during the reaction, but when isolated **2** could be cyclized using phosphoric acid.

The mechanism of the Nazarov cyclization was described incorrectly for several years following its discovery. Braude and Coles[2] studied the reaction and in 1953 proposed a mechanism with a carbocation intermediate (Figure 1.2). The dienone **4** can be protonated or complexed with a Lewis Acid, generating **5** in a reversible equilibrium. From the resonance contributor **6**, a 4π electron conrotatory electrocyclization takes place

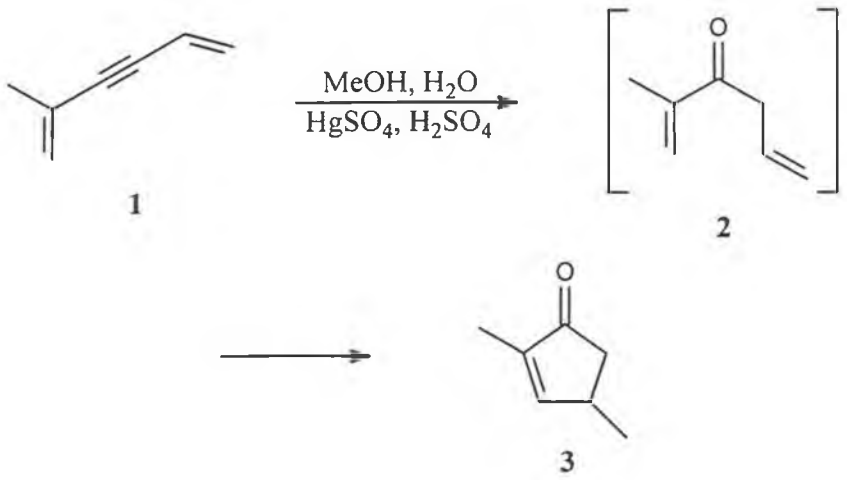



**Figure 1.1.** Hydration and cyclization of dienynes.

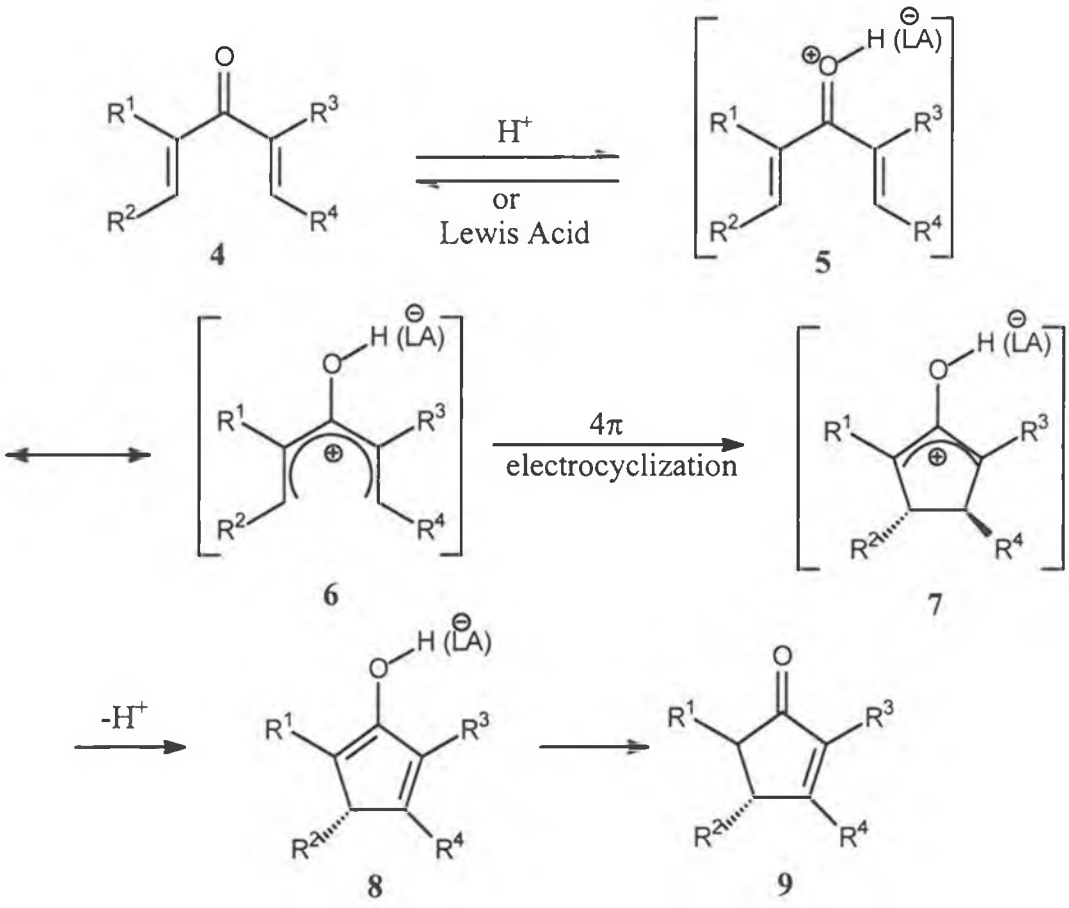



**Figure 1.2.** Mechanism of the Nazarov cyclization.

to generate oxyallyl carbocation **7**. Deprotonation followed by tautomerization of the resulting enol **8** generates cyclopentenone **9**. The deprotonation step typically furnishes the thermodynamically most stable olefin.

Placing a trialkylsilyl group at one of the β-positions permits access to the thermodynamically less stable olefin (Figure 1.3). These cyclizations have been termed silicon-directed Nazarov cyclizations.[3] Silyl groups are valuable substituents in the Nazarov cyclization due to their ability to stabilize β-cations.[4] Once the cyclization has transpired to form the cation **12**, the silyl group is stereoelectronically aligned to allow nucleophile-assisted desilylation, forming the less stable olefin. Tin-directed Nazarov cyclizations occur in much the same fashion when a trialkyltin group is placed β to the ketone.[5]

One unique way to take advantage of the mechanistic features of the cyclization is by trapping the oxyallyl carbocation intermediate with a nucleophile. West and coworkers[6] have investigated the photochemical reaction of various 4-pyrone systems (Figure 1.4). 4-Pyrones such as **15** contain a dienone system similar to that of Nazarov substrates, but contained within the six-membered heterocycle. Since cyclization of these dienones can only occur in a disrotatory fashion, photochemical conditions are required to generate the cyclopentenone. Cyclization proceeds through the oxyallyl zwitterion **16**. In the presence of a nucleophilic solvent, trapping of the carbocation by methanol occurs at both carbocationic positions to generate two methanol-incorporated products, **17** and **18**, in a 2:3 ratio.

Nucleophilic addition to an oxyallyl carbocation can also occur after a thermally allowed cyclization.[7] Cyclization of dienone **19** results in the unexpected cyclopentenone

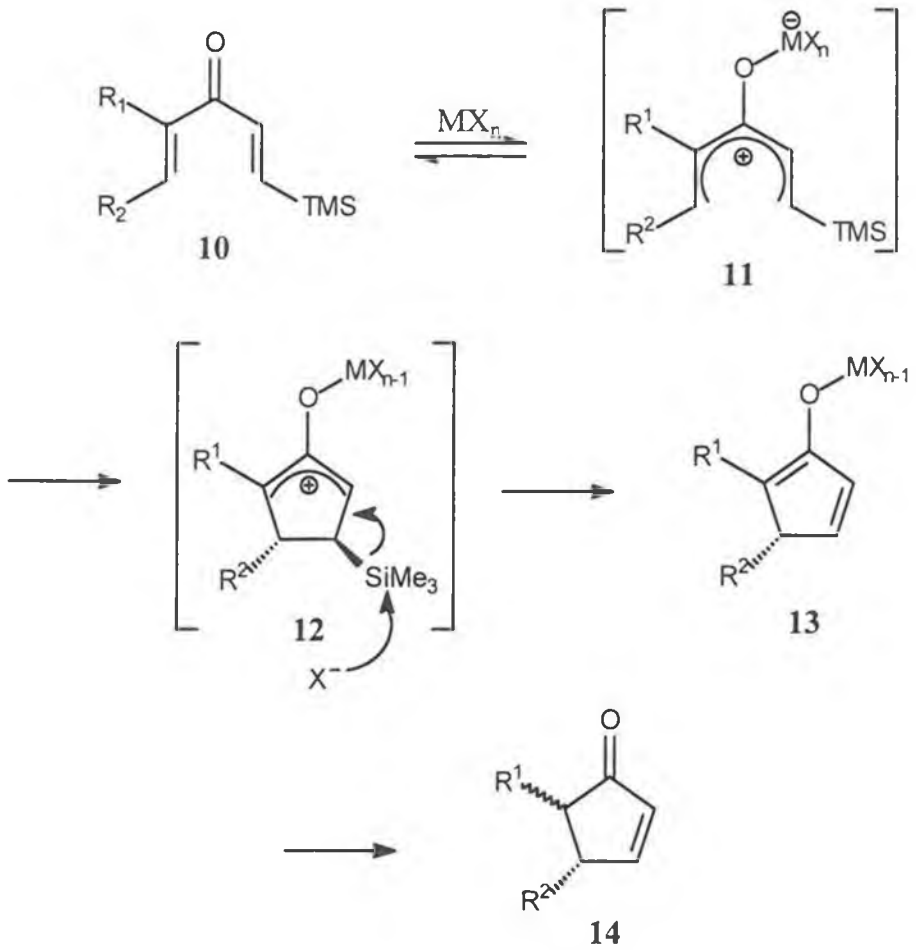



**Figure 1.3.** The silicon-directed Nazarov cyclization.

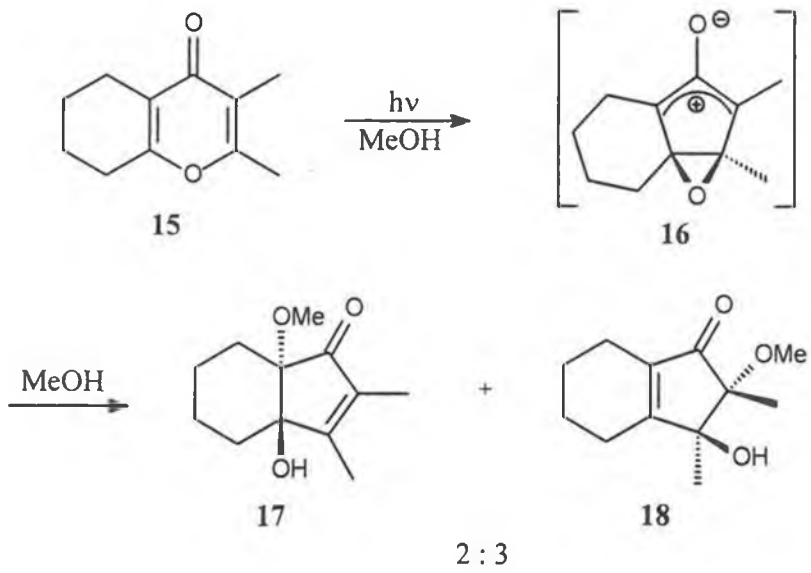



**Figure 1.4.** Photocyclization and solvent trapping.

**26** by a mechanism starting with trapping of the oxyallyl carbocation **21** by water to form **22** (Figure 1.5). Tautomerization to form the more stable enol **23** followed by elimination of the hydroxyl group at $C^1$ generates the new oxyallyl carbocation **24**. Tautomerization to form carbocation **25** followed by deprotonation yields the observed cyclopentenone **26**.

The intermediate carbocation in the Nazarov cyclization also has the potential for rearrangements. Motoyoshiya and coworkers studied the cyclization of various dienones such as **27**, which produced cyclopentenones such as **34** as a result of a Wagner-

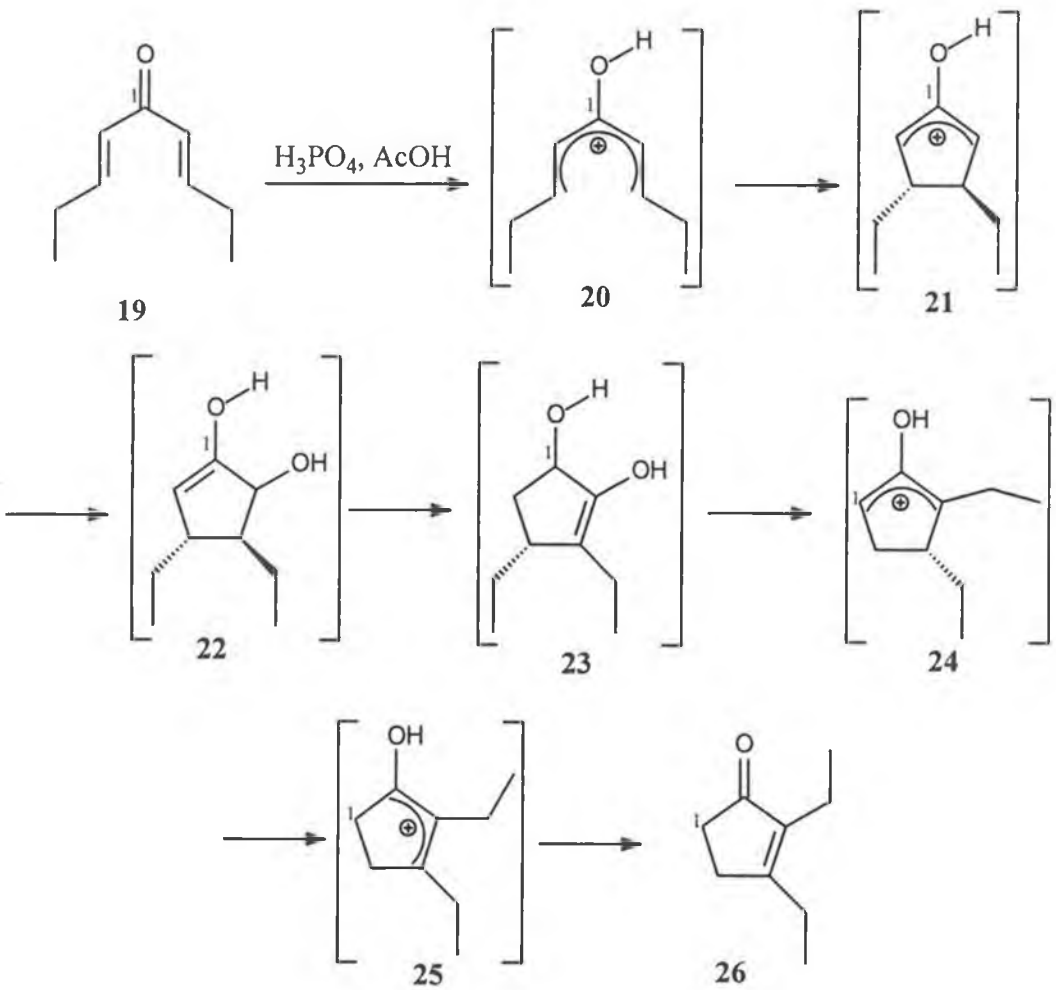



**Figure 1.5.** Solvent trap and rearranged cyclopentenone.

Meerwein shift (Figure 1.6).[8] Such a rearrangement is possible under harsh acidic reaction conditions. Conrotatory cyclization generates intermediate **29**, which can be deprotonated to form **30**. The strongly acidic conditions permit reprotonation of **30**, forming the new oxyallyl carbocation **31**. A 1,2-shift of one of the methyl groups generates the new carbocation **32**, which leads to the final Nazarov product after deprotonation and quenching. Generation of Wagner-Meerwein products was minimized when milder cyclization conditions were used.

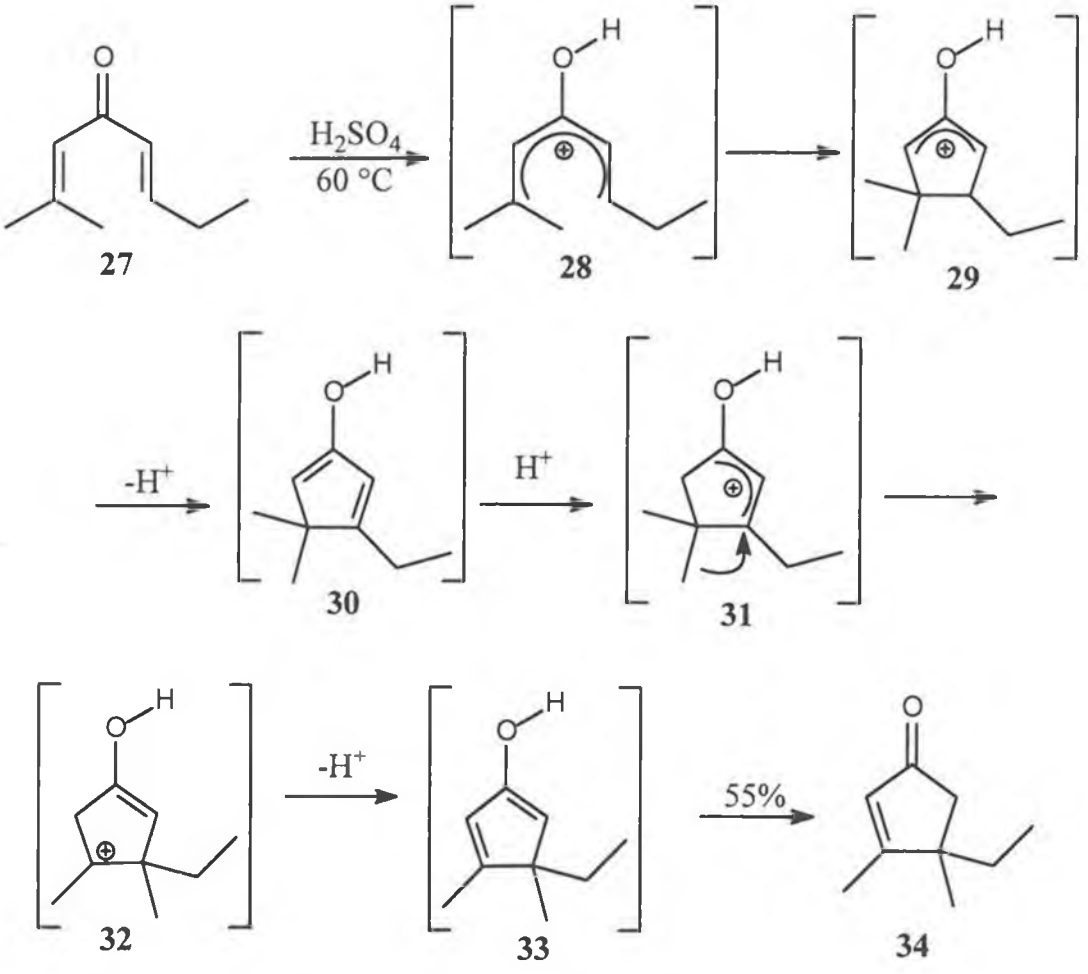



**Figure 1.6.** Wagner-Meerwein shift during the Nazarov cyclization.

Solvents are not the only nucleophilic components that can add to the oxyallyl carbocation. The interrupted Nazarov cyclization can ensue when a pendant nucleophile traps the oxyallyl carbocation resulting from the 4π electrocyclization (Figure 1.7). An example studied by West and coworkers employed substrate **35**, which includes an olefin connected by a two-carbon tether.[9] Oxyallyl carbocation **37** was trapped by the pendant olefin generating a tertiary carbocation, **38**. A third ring was generated when the enolate oxygen trapped the carbocation followed by hydration of the strained enol ether during aqueous work-up to form the hemiketal **40** as a single diastereomer.

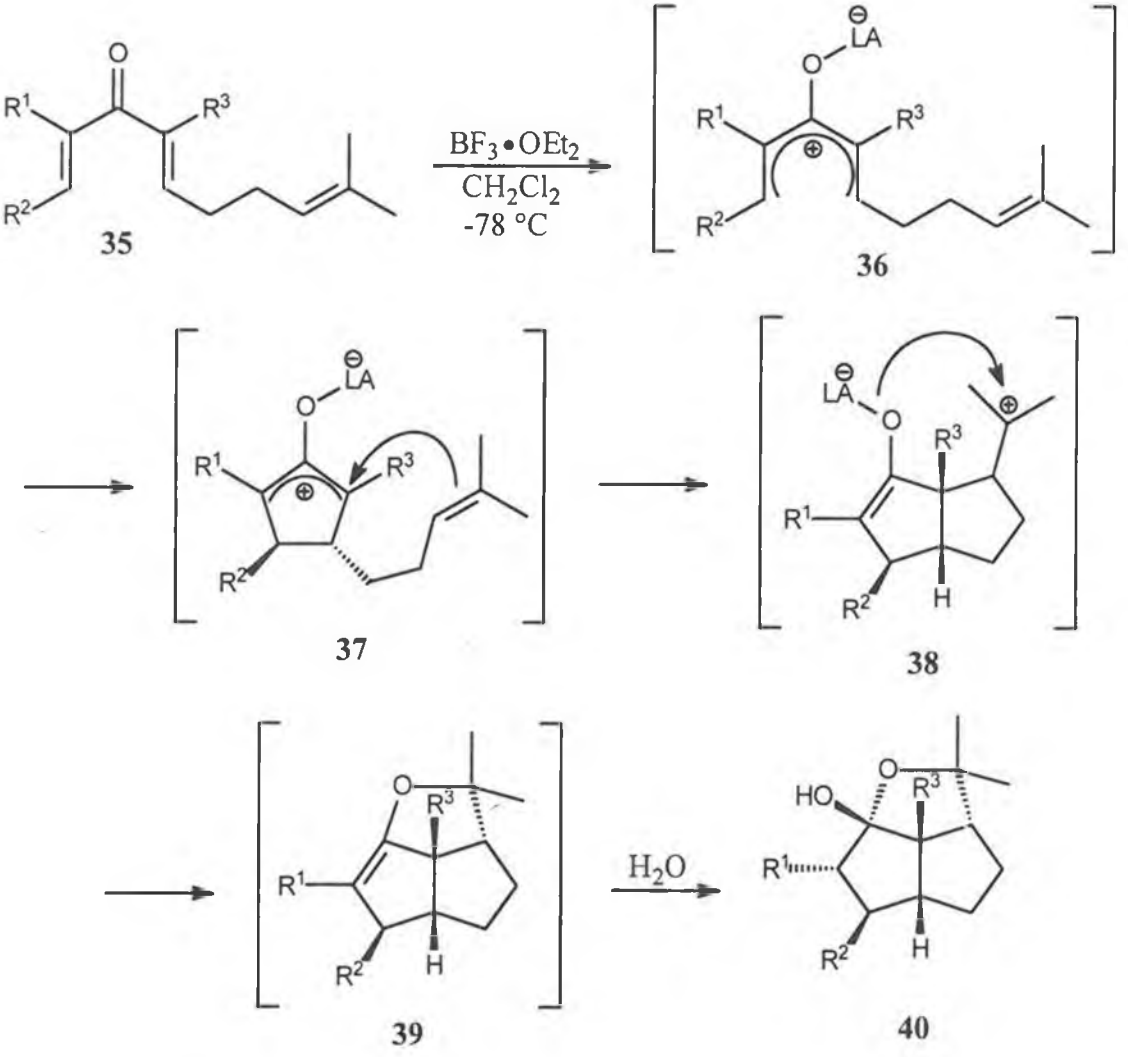
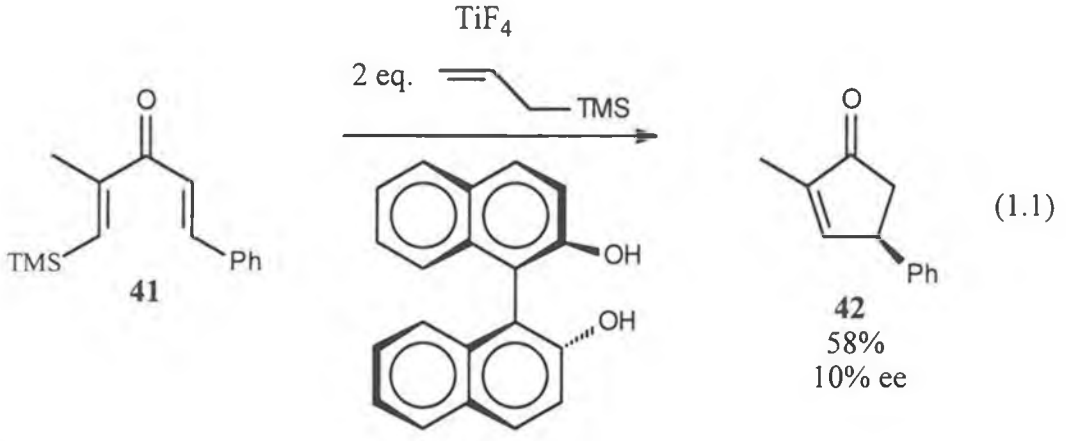



**Figure 1.7.** The interrupted Nazarov cyclization.

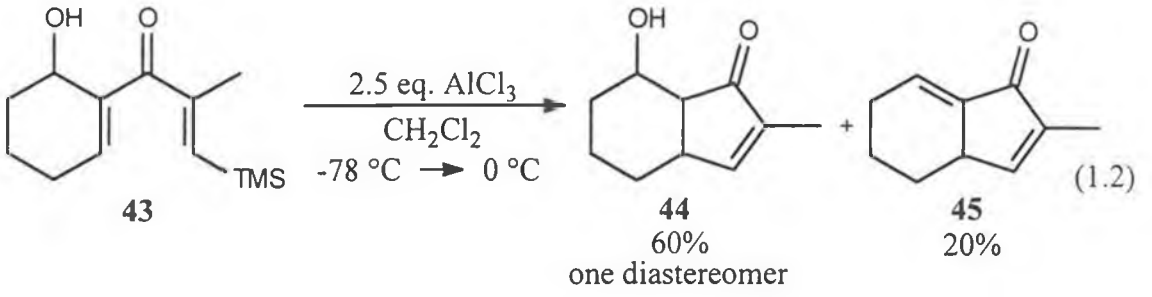
Predictable stereochemistry is a very important aspect of synthetic organic chemistry, and has been addressed in the Nazarov cyclization in several ways. One method is the use of chiral Lewis Acids in an attempt to favor conrotatory rotation in one direction during the cyclization, creating an enantiomerically enriched product.[10] Preliminary results using a $TiF_4$/BINOL complex do not show extraordinary enantioselectivity. Silicon-directed Nazarov cyclization of substrate **41** in the presence of the chiral Lewis acid generates the product **42** in only 10% ee (Eq. 1.1). Studies are currently underway to determine if other chiral Lewis Acids are more effective in the enantioselective cyclization of simple substrates like **41**.




(1.1)

More complex starting materials may provide a handle to help generate selectivity. Chelation effects have been used in many reactions to generate a specific stereo or regioisomer.[11] Early studies by West and coworkers on the possibility of a chelation controlled Nazarov cyclization have been promising.[12] Compound **43**, containing an allylic hydroxyl group, was chosen for the first study (Eq. 1.2). If a Lewis Acid could initiate the reaction and chelate with the alcohol, selectivity might be observed. Upon cyclization with $AlCl_3$, products **44** and **45** were formed. Compound **45** is the result of elimination following the initial cyclization. The major product, however,

is observed as only one diastereomer, indicating that the chirality of the molecule determined the stereochemical outcome of the cyclization. Stereoselectivity such as this resulting from a remote chiral center has been termed torquoselectivity.[13]




**43**

**44**
60%
one diastereomer

**45**
20%

A remote chiral substituent can favor one conrotatory cyclization over the other generating one product preferentially in other systems as well. One such example studied by Mehta and Khrishnamurthy was the cyclization of dienone **46** (Figure 1.8).[14] Torsional and nonbonded interactions present within the molecule before and during the cyclization generate a preferred conformation resulting in a greater percentage of one product over the other. Conformation **47** is favored over **48** due to interactions of the protonated carbonyl with the diquinane ring system. Placing $H^1$ over $H^2$ in intermediate **48** positions the protonated carbonyl in close proximity to the five-membered ring. However, **47** avoids this interaction by placing the oxygen under the ring system. Conrotatory closure of **47** leads to the major product **49** after deprotonation. If the facial bias between the α and β faces of the fused ring system were more distinct, the selectivity seen here (4:1) could potentially be improved.

Denmark and coworkers have studied silicon-directed Nazarov cyclizations exhibiting very good torquoselectivity.[15] Chiral substrate **51** was synthesized to take

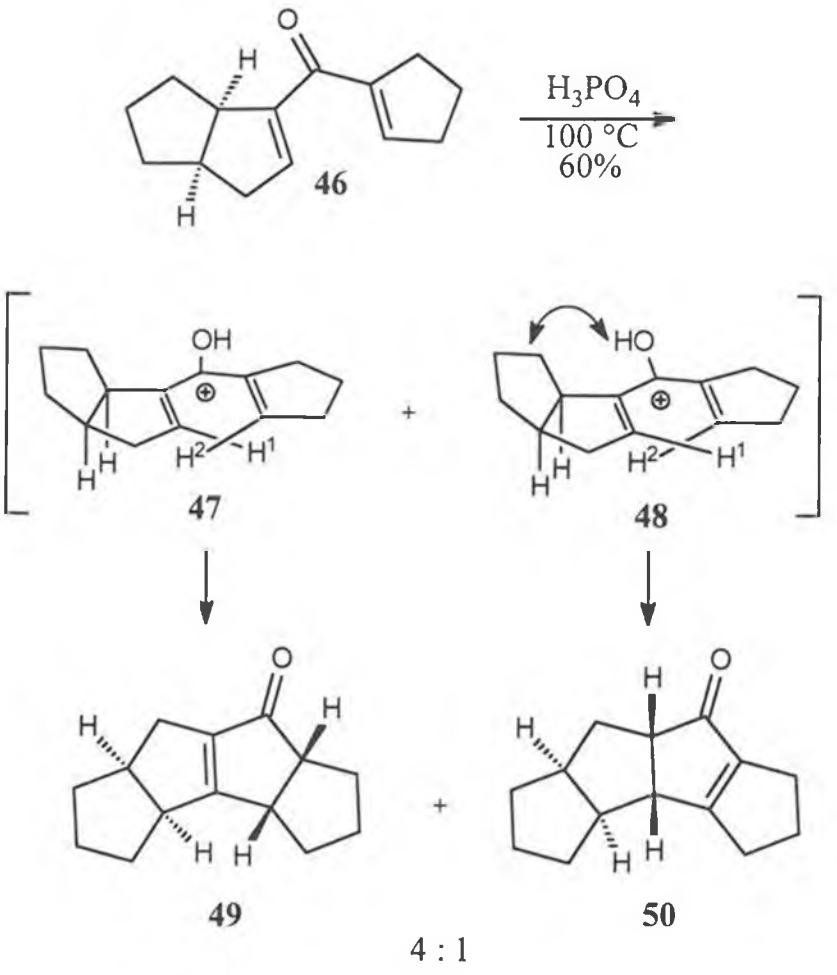



**Figure 1.8.** Torquoselective formation of a tetraquinane.

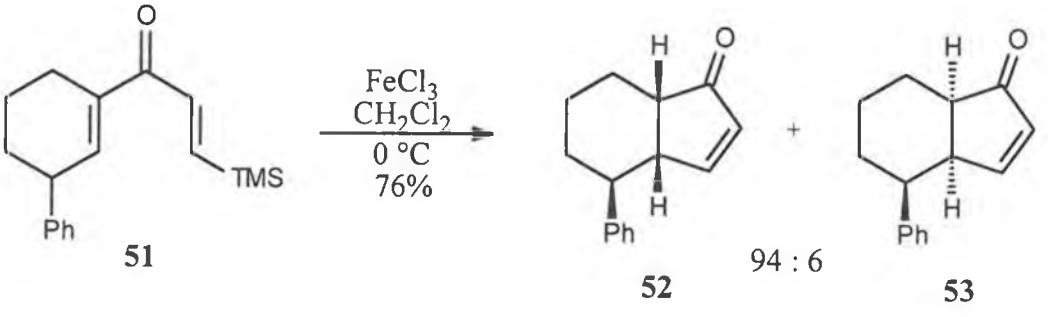



**Figure 1.9.** Torquoselective silicon-directed Nazarov cyclization.

advantage of the remote chiral center at $C^1$ (Figure 1.9). Chirality at this center controlled torquoselectivity very effectively. $FeCl_3$ cyclization of the starting material at 0 °C generated diastereomers **52** and **53** in a ratio of 94:6.

A cyclization by Tsuge and coworkers yielded excellent torquoselectivities.[16] Cyclization of the chiral diester **54** in the presence of $GaCl_3$ generated only one diastereomer **55** in good yield, along with minor amounts of isomer **56** (Figure 1.10). Interactions on one face of the ring result in preferential cyclization to form **55**.

Control of the Nazarov cyclization via the use of chiral starting materials is an exceptionally promising solution to generating stereoselectivity. The availability and affordability of simple chiral starting materials which can be fuctionalized to generate dienones makes this method very appealing. The following chapter will describe the synthesis of such substrates and the selectivity they exhibit resulting from the Nazarov cyclization.

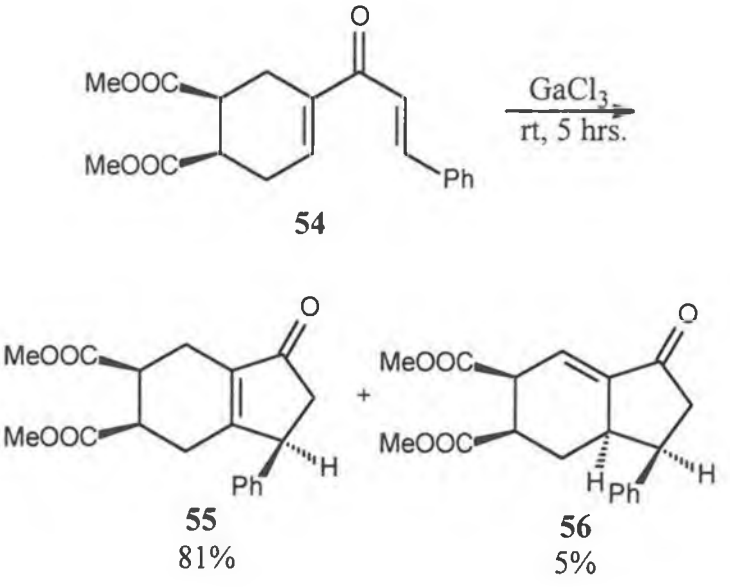



**Figure 1.10.** Chiral diester allows only one conrotatory cyclization.

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# Chapter 2

## TORQUOSELECTIVITY AND CHLORIDE TRAPPING IN THE NAZAROV CYCLIZATION

### Introduction

The prominence of the cyclopentanoid framework in natural products has created a necessity to form this ring system efficiently.[1] The Nazarov cyclization is an important method to form this common ring system.[2] The previous chapter discussed several ways to control stereochemistry during the cyclization. One of the more interesting methods to control stereochemistry is the utilization of effects which induce twisting in a predictable fashion, called torquoselectivity. Stereoselectivity ranged from good to excellent based solely on steric interactions during the cyclization. Many of the substrates, exhibiting good torquoselectivity, were complex compounds requiring several steps to synthesize. Therefore, a good method would begin with a readily available starting material, functionalization to the required dienone in a minimum number of steps, and finally torquoselective cyclization. Several examples fitting these criteria will be discussed in the remainder of this chapter.

Two readily available bicyclic systems chosen for study were the bicyclo[2.2.1]heptane system of camphor (**1**), and the bicyclo[3.1.1]heptane system


**1** **2** **3**

**Figure 2.1.** Facially biased starting materials.

contained in nopinone (**2**) and myrtenal (**3**) (Figure 2.1). The α and β faces in both these systems are very different from one another. If both these starting materials could be fuctionalized to make dienones such as **4**, the torquoselective effects the bridged bicyclic systems impose during the Nazarov cyclization could be studied (Figure 2.2). The inherent conrotatory nature of the cyclization would require either an *exo*-type intermediate **5** or an *endo* intermediate **6**. Deprotonation to form the thermodynamically stable olefin, followed by quenching of the enolate would generate products **7** and **8**.

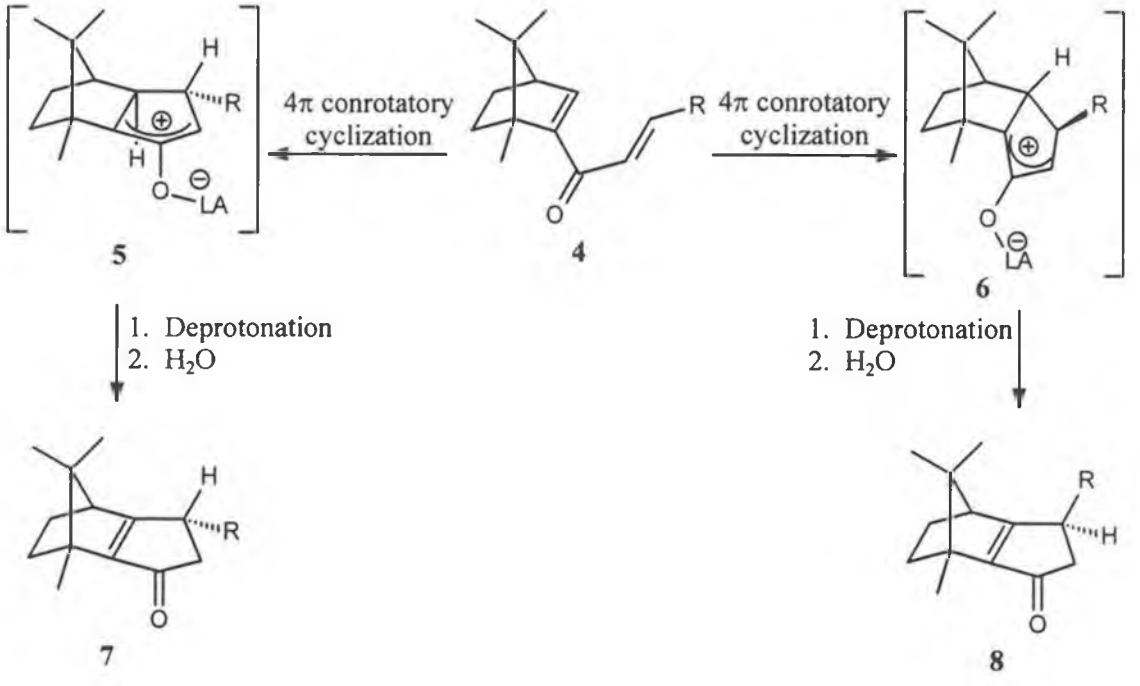
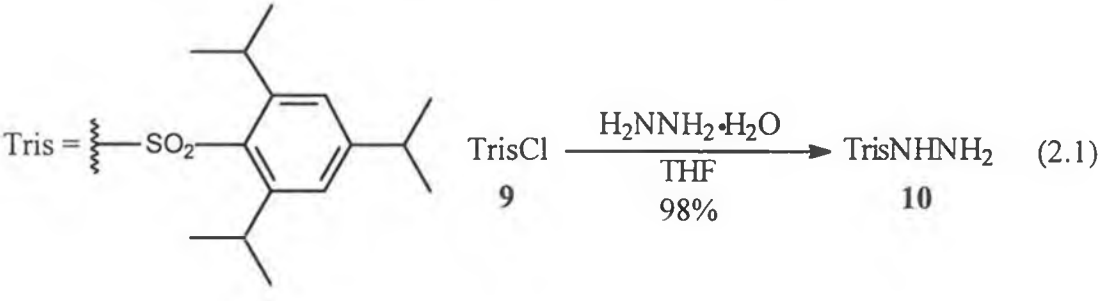



**Figure 2.2.** Proposed cyclization of facially biased dienones.

## Preparation of Dienones

In order to generate the desired dienones from camphor, it was necessary to transform the ketone into a hydrazone. First, trisyl chloride was converted to the trisyl hydrazide **10** by reaction with hydrazine hydrate in THF (Eq. 2.1),[3] which was reacted with camphor in the presence of concentrated HCl to yield hydrazone **11** in low yields after recrystalization (Figure 2.3).[4] Yields were improved slightly by crystallizing a second crop from the mother liquor, but yields were still quite low. A Shapiro reaction with this hydrazone generated a dienol, which was oxidized to the appropriate dienone. Trisyl hydrazone in the presence of two equivalents of *sec*-BuLi forms a vinyl anion, which was treated with several α,β-unsaturated aldehydes to form the desired dienols **13**. Oxidation of these dienols was accomplished with $BaMnO_4$ to generate dienones **14**.




Most α,β-unsaturated aldehydes used for the Shapiro reaction were commercially available. Two exceptions are the extremely volatile aldehydes **12a** and **12d** (Figures 2.4 and 2.5). The synthesis of these aldehydes, although straightforward, is worth noting because they had an important effect on subsequent steps. In most cases these aldehydes were taken on crude to minimize loss of material due to evaporation, and the consequent impurity led to reduced yields in the Shapiro reaction.

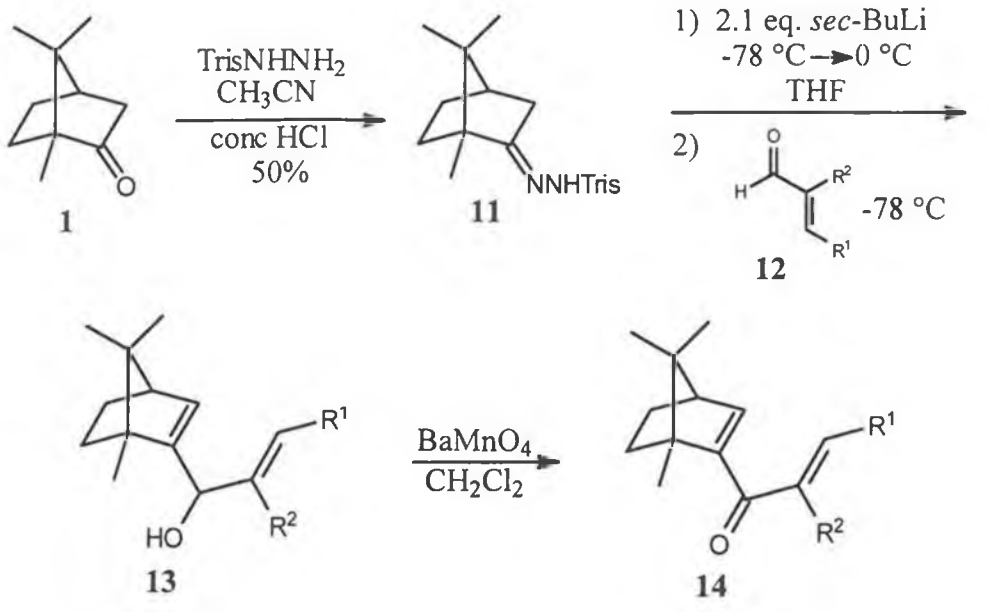



**Figure 2.3.** Synthesis of facially biased dienones.

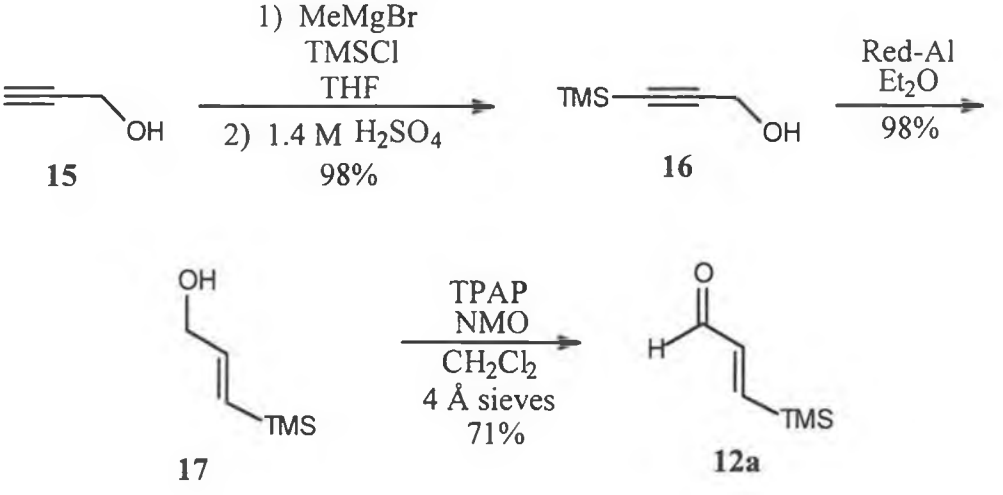



**Figure 2.4.** Synthesis of aldehyde **12a**.

Aldehyde **12a** was prepared by deprotonation of propargyl alcohol followed by addition of two equivalents of TMSCl.[5] Acidic workup to deprotect the alcohol generated compound **16**. Selective reduction with Red-Al yielded exclusively the *E* alcohol **17**. Oxidation with TPAP and NMO[6] generated the desired aldehyde after filtration of the reaction mixture through Celite.

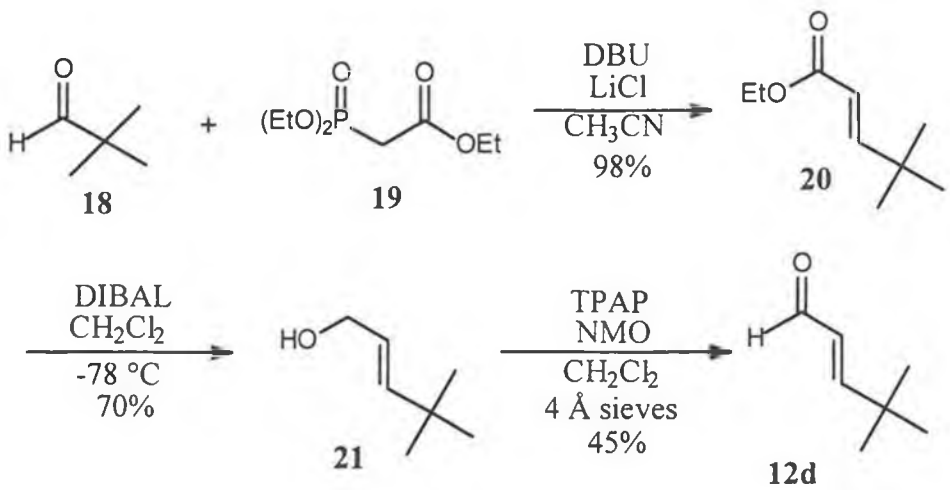



**Figure 2.5.** Synthesis of aldehyde **12d**.

t-Butyl aldehyde **12d** was generated starting with a Horner-Emmons reaction with pivalaldehyde to generate ester **20**.[7] DIBAL reduction to form alcohol **21** followed by TPAP oxidation generated the desired aldehyde.[8] As expected, this aldehyde was even more volatile than **12a**, so great care was taken during isolation. After the reaction mixture was plugged through Celite, the aldehyde was concentrated *in vacuo*, while the flask containing the aldehyde was cooled to -10 °C, until a minimum amount of solvent remained. The aldehyde was taken on crude, still dissolved in a small amount of the original reaction solvent.

Several conditions for the Shapiro reaction were attempted with limited success.[9] Halterman discovered that when *sec*-BuLi was used as the base and tetrahydrofuran was the solvent, Shapiro reactions were quite successful with trisyl hydrazone **11**.[10] Indeed, yields were greatly improved for all reactions; however, aldehyde purity was still the limiting factor for success of the reaction (Table 2.1). With the dienols **13a-e** in hand, oxidation was originally attempted with TPAP in the presence of NMO, which resulted in no reaction. Denmark had successfully oxidized several dienols to dienones with

$BaMnO_4$.[11] These conditions worked very well for dienols **13a-e** as well (Table 2.1). The only drawback of this method is the requirement for ten equivalents of the oxidizing agent to complete the reaction. In some cases it was possible to use only five equivalents if the reaction time was increased.

**Table 2.1.** Yields of dienols and dienones.

| dienol | $R^1$ | $R^2$ | yield | dienone | yield |
|---|---|---|---|---|---|
| **13a** | TMS | H | 25% | **14a** | 70% |
| **13b**[10] | Ph | H | 80% | **14b** | 75% |
| **13c**[10] | $CH_3$ | H | 50% | **14c** | 80% |
| **13d** | t-butyl | H | 50% | **14d** | 88% |
| **13e** | Ph | $CH_3$ | 80% | **14e** | 80% |

Synthesis of substrates containing the bicyclo[3.1.1]heptane system of myrtenal and nopinone proved to be convenient because these two compounds allowed preparation of dienols by two different methods. Commercial availability of some Grignard reagents provided a method to avoid some of the problematic Shapiro reactions, while readily available aldehydes could still be used with the hydrazone of nopinone.

Hydrazone **22** was prepared by the same method as the camphor case except for a slight modification during isolation (Figure 2.6). Table 2.2 outlines the yields of the Shapiro reaction of **22** with various aldehydes. The commercially available bromide of **25** and Grignard reagent **27** allowed an easy approach to dienols from myrtenal (Figure 2.7).[12] No attempt was made to separate the four diastereomers of compound **23c** and they were oxidized crude. Again, $BaMnO_4$ was used to oxidize dienols **23a-e** (Table 2.3). The *Z* and *E* isomers resulting from the oxidation of **23c** could now be separated using medium pressure liquid chromatography.

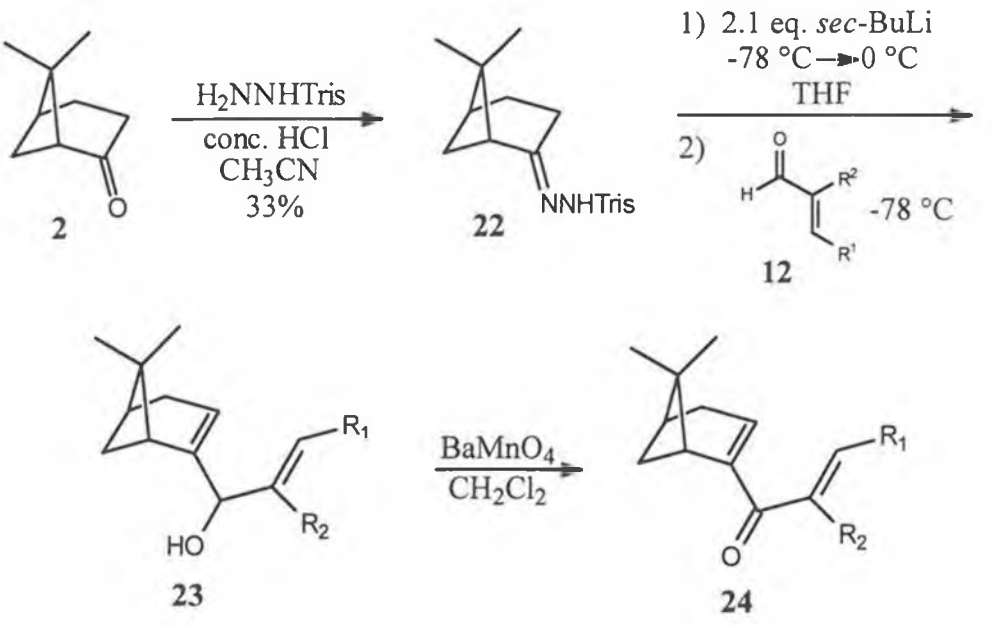



**Figure 2.6.** Synthesis of dienones from nopinone.

**Table 2.2.** Results of Shapiro reactions.

| dienol | $R^1$ | $R^2$ | yield |
|---|---|---|---|
| **23b** | Ph | H | 80% |
| **23e** | Ph | $CH_3$ | 86% |

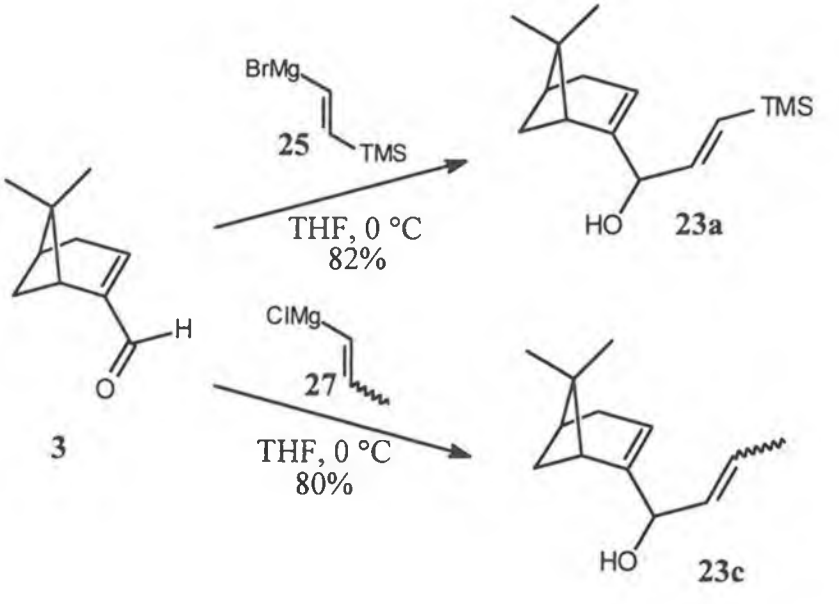


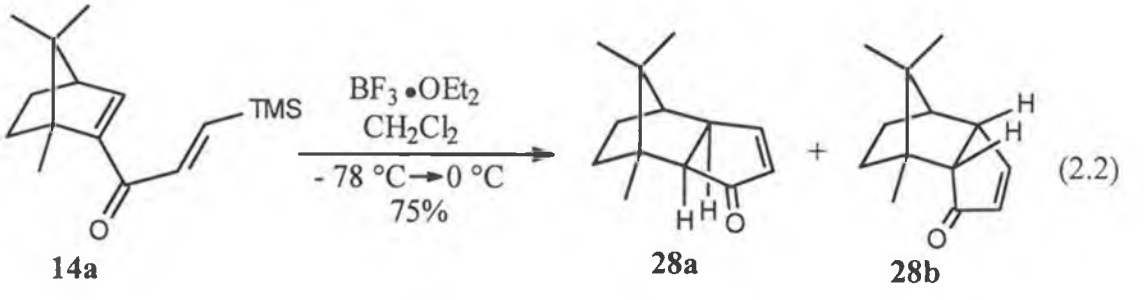

**Figure 2.7.** Synthesis of dienols via Grignard reactions

**Table 2.3.** Results of $BaMnO_4$ oxidation of dienols.

| dienone | $R^1$ | $R^2$ | yield |
|---|---|---|---|
| **24a** | TMS | H | 70% |
| **24b** | Ph | H | 54% |
| **24c** | *Z*-$CH_3$ | H | 41% |
| **24d** | *E*-$CH_3$ | H | 41% |
| **24e** | Ph | $CH_3$ | 83% |

Cyclization of Nazarov Substrates

Cyclization of silicon-containing dienone **14a** was examined first (Eq. 2.2). $BF_3$•$OEt_2$ is a frequently used Lewis Acids for the silicon-directed Nazarov cyclization,[13] making it a logical choice for this substrate. Treatment of **14a** with four equivalents of $BF_3$•$OEt_2$ at -78 °C provided no reaction by thin layer chromatography (TLC). The reaction was warmed to 0 °C and allowed to stir overnight. Isolation of the major products furnished compound **28** as a 10:1 mixture of diastereomers as seen by $^1H$ NMR in 75% yield. It was possible to partially separate the diastereomers using careful radial




**14a** **28a** **28b** (2.2)

chromatography procedures. Nuclear Overhauser Effect Spectroscopy (NOESY) of the major product showed interactions expected for the *exo* product. Proton assignments were based on coupling constants and Correlated Spectroscopy (COSY). Interactions between the gem dimethyl and bridgehead protons were not observed and Figure 2.10 and Table 2.4 illustrate the observed interactions used to make the stereochemical

assignment. $H^d$ and $H^e$ were identified by their interactions with methyl group protons i. Once these protons were identified, $H^f$ and $H^g$ were easy to determine. These are the key protons, which show interactions with the bridgehead protons supporting the *exo* stereochemical assignment.

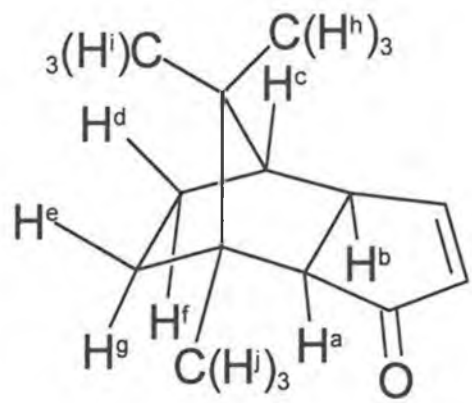



**Figure 2.8.** Structure of compound **28a**.

**Table 2.4.** NOESY interactions in compound **28a**.

| | | $H^a$ | $H^b$ | $H^c$ | $H^d$ | $H^e$ | $H^f$ | $H^g$ | $H^h$ | $H^i$ | $H^j$ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | δ | 2.13 | 2.80 | 1.97 | 1.86 | 1.59 | 1.19 | 1.30 | 0.72 | 0.78 | 1.15 |
| $H^a$ | 2.13 | | X | | | | X | X | | | |
| $H^b$ | 2.80 | X | | | | | X | | | | |
| $H^c$ | 1.97 | | | | | | | | X | X | |
| $H^d$ | 1.86 | | | | | X | X | | | | |
| $H^e$ | 1.59 | | | | X | | | X | | | |
| $H^f$ | 1.19 | X | X | | X | | | | | | |
| $H^g$ | 1.30 | X | | | | X | | | | | |
| $H^h$ | 0.72 | | | X | | | | | | X | X |
| $H^i$ | 0.78 | | | X | | | | | X | | X |
| $H^j$ | 1.15 | | | | | | | | X | X | |

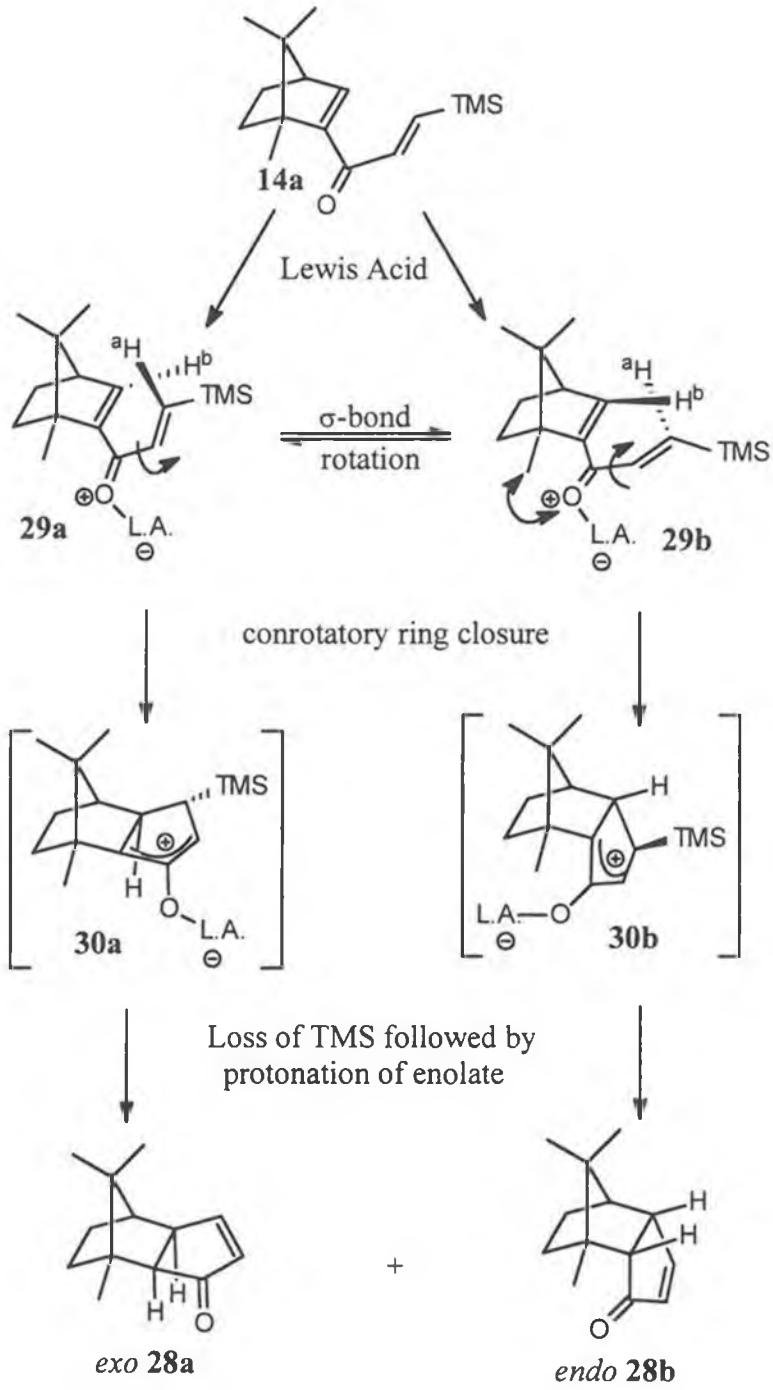
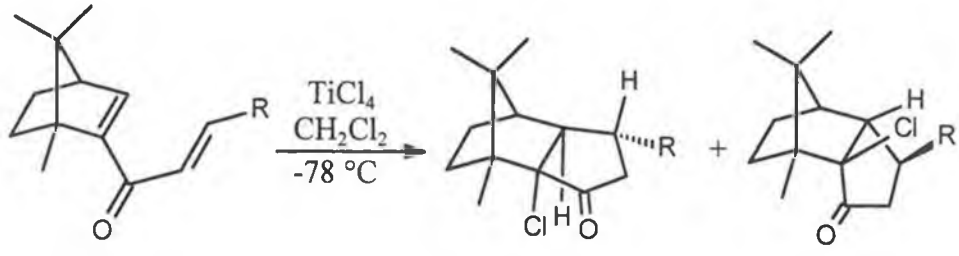



**Figure 2.9.** Steric interactions during cyclization of **14a**.

Torquoselectivity determines the stereochemistry resulting from cyclization of substrate **14a** (Figure 2.9). Intermediates **29a-b** show after complexation, as the substrate approaches cyclization, steric interactions between the bridgehead methyl group and the carbonyl leads to a preference for **29a** over **29b**. As a consequence, this places proton a above proton b. Conrotatory cyclization then occurs such that the vinyl protons are not required to pass each other. Cyclization of **29a** followed by silicon directed formation of the less substituted olefin and protonation of the enolate yields *exo* product **28a**. By the same analogy, placing proton b over proton a in **29b** generates the *endo* product following the conrotatory cyclization.

The excellent results of the silicon directed substrate held great promise for cyclization of the remaining substrates. Several Lewis Acids were used to cyclize substrate **14b** on small scale. After isolation of products from the reactions of $BF_3{\cdot}OEt_2$, $SnCl_4$, $TiCl_4$ and $FeCl_3$ several unusual products were observed. The desired product containing a tetrasubstituted olefin was not observed in any of these cyclizations. Cyclization with $TiCl_4$ provided one of the cleanest reactions, so it was chosen for further study (Eq. 2.3). Mass spectroscopy determined that a chlorine atom was present in the




(2.3)

**14** ***exo* 31** ***endo* 32**

final product. Upon cyclization, the oxyallyl carbocation was trapped by a chloride nucleophile before deprotonation could occur. This is not the first example of chlorine

trapping of oxyallyl type carbocations.[14] Denmark also observed chlorine incorporation during a Nazarov cyclization.[15] However, he observed quenching of the enolate by a chlorine electrophile, not the nucleophilic trapping observed here. Again a combination of coupling constants, COSY and NOESY methods allowed the assignment of the

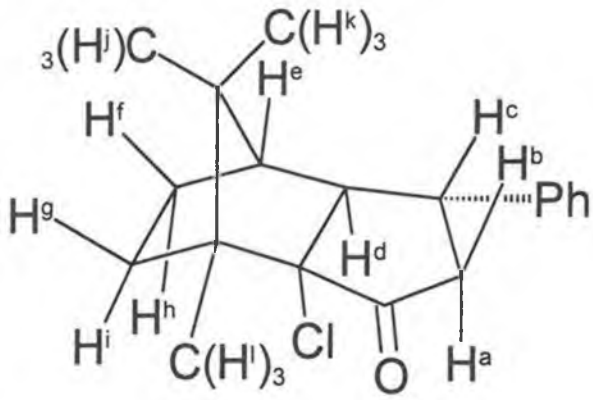



**Figure 2.10.** Structure of compound **31b**.

**Table 2.5.** NOESY interactions observed in **31b**.

| | | $H^b$ | $H^c$ | $H^d$ | $H^e$ | $H^f$ | $H^g$ | $H^h$ | $H^i$ | $H^j$ | $H^k$ | $H^l$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | δ | 2.81 | 3.23 | 2.38 | 1.91 | 1.81 | 1.40 | 1.21 | 2.18 | 0.96 | 0.88 | 1.19 |
| $H^b$ | 2.81 | | X | | | | | | | | | |
| $H^c$ | 3.23 | X | | | X | | | | | | X | |
| $H^d$ | 2.38 | | | | | | | X | | | | |
| $H^e$ | 1.91 | | X | | | | | | | X | X | |
| $H^f$ | 1.81 | | | | | | | X | | X | | |
| $H^g$ | 1.40 | | | | | | | | X | X | | X |
| $H^h$ | 1.21 | | | X | | X | | | | | | |
| $H^i$ | 2.18 | | | | | | X | | | | | X |
| $H^j$ | 0.96 | | | | X | X | X | | | | | X |
| $H^k$ | 0.88 | | X | | X | | | | | | | X |
| $H^l$ | 1.19 | | | | | | X | | X | X | X | |

structure and stereochemistry of **31b** with some degree of confidence. As with the silicon directed example, the *exo* product is favored and was the only diastereomer isolated in 88% yield. Chloride traps at the more stable tertiary carbocation, although this site is more hindered. Figure 2.10 and Table 2.5 display the interactions key to determining the stereochemistry of the product. $H^g$ and $H^h$ were identified because of interactions with methyl group protons j. This identifies $H^h$, which shows an interaction with $H^d$. This interaction, as well as the interaction of proton $H^c$ and methyl group protons k, supports the *exo* stereochemical assignment.

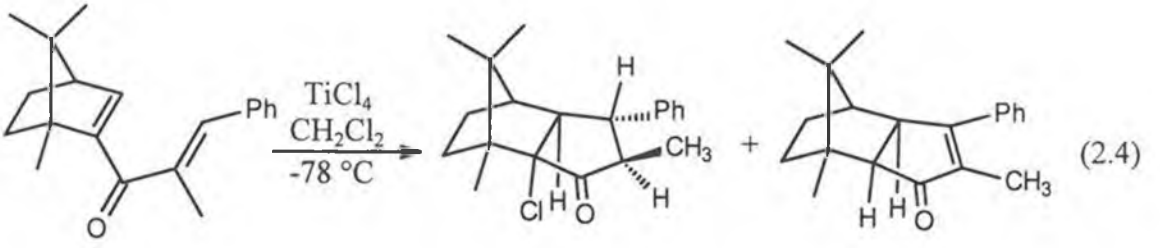
Cyclization of substrates **14c** and **14d** also exhibited the same chloride trapping (Table 2.6). In both cases however, the selectivity for the *exo* product was decreased. Substrate **14c** was cyclized in 66% yield but the ratio of *exo* to *endo* diastereomers was 8:1. More importantly, the t-butyl case also went in 66% yield, but only a 3:1 ratio of *exo* over *endo* products.

**Table 2.6.** Ratios and yields of chloride trapped products.

| | cyclized product | | |
|---|---|---|---|
| dienone | *exo* **31** | *endo* **32** | yield |
| **14b** | 1 | 0 | 88% |
| **14c** | 8 | 1 | 66% |
| **14d** | 3 | 1 | 66% |

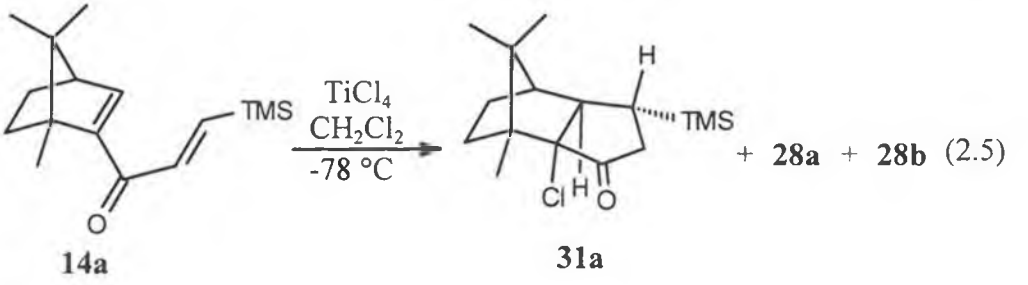
Substrate **14e** was subjected to the $TiCl_4$ reaction conditions and was very reactive (Eq. 2.4). The solution turned a very deep reddish-brown and starting material was consumed after only ten minutes at -78 °C. The enhanced reactivity observed for substrate **14e** allowed formation of polymeric products and decreased yields of cyclized products to 50%. Two products **31e** and **33** were recovered in a 1:1 ratio. Two-

dimensional spectroscopy proved that both structures were the result of an *exo* cyclization, but formation of the tetrasubstituted olefin in **33** was able to compete with chloride trapping. Presumably, no ring-fusing tetrasubstituted olefins were seen in earlier cases because of strain. However, this example allows olefin formation away from the ring-fusion. Lower reaction temperatures (-100 °C) and less than one equivalent of Lewis Acid were tried to decrease the amount of polymeric material, but no improvement was observed.




**14e** **31e** **33**

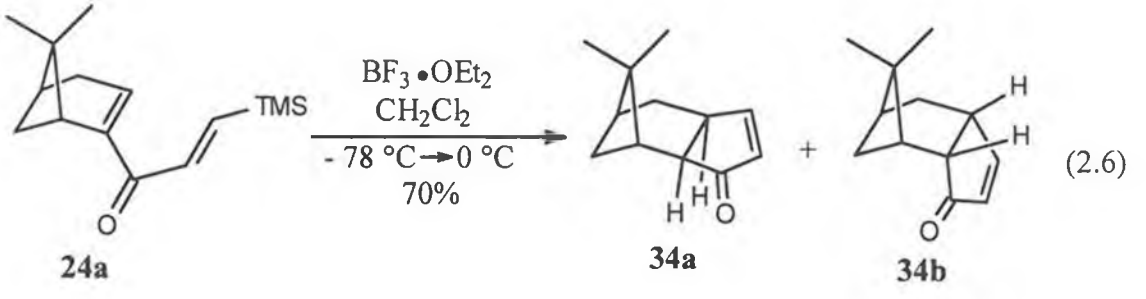
Silicon-containing substrate **14a** was also cyclized with $TiCl_4$ (Eq. 2.5). Starting material was consumed much faster than in the $BF_3 \cdot OEt_2$ reaction and two major products were observed by TLC. Product isolation revealed a 43% yield of the expected products **28a** and **28b**; however, the ratio of *exo* to *endo* products had decreased to 6:1. The other product was the chloride adduct **31a** isolated in 31% yield. Two-dimensional spectroscopy supported an *exo* stereochemical assignment for the chloride trapped product, indicating that the cyclization had actually occurred in a 10:1 ratio as before; however, a portion of the *exo* product was trapped by chloride before the silicon-directed elimination could occur. A portion of the *endo* intermediate was probably trapped also, but in quantities small enough that it was not isolated.




**14a** **31a**

+ **28a** + **28b** (2.5)

Cyclization of silylated substrate **24a** was the first myrtenal-based substrate examined (Eq. 2.6). Four equivalents of $BF_3 \bullet OEt_2$ were added to **24a**, and after seventeen hours at -20 °C starting material was consumed. Diastereomers **34a** and **34b** were isolated in a 70% yield and $^1H$ NMR showed a disappointing 2:1 ratio of isomers. More interestingly, isolation and characterization by two-dimensional NMR of the major diastereomer strongly suggested that it was actually the *endo* product **34b**.




**24a** **34a** **34b**

(2.6)

While both the camphor and myrtenal systems seem to be closely related, there is one important difference. The bridgehead methyl group, which is absent in myrtenal, may be critical to the *exo* selectivity in the camphor case. The facial bias of myrtenal affects stereochemistry in a different way (Figure 2.11). The gem dimethyl group is too distant to affect the carbonyl in either a negative or positive manner. However, **35a** shows the disfavored interaction between proton a and one of the methyl groups. This interaction is not as severe as the carbonyl bridgehead methyl interaction seen for camphor, therefore selectivity is only moderate.

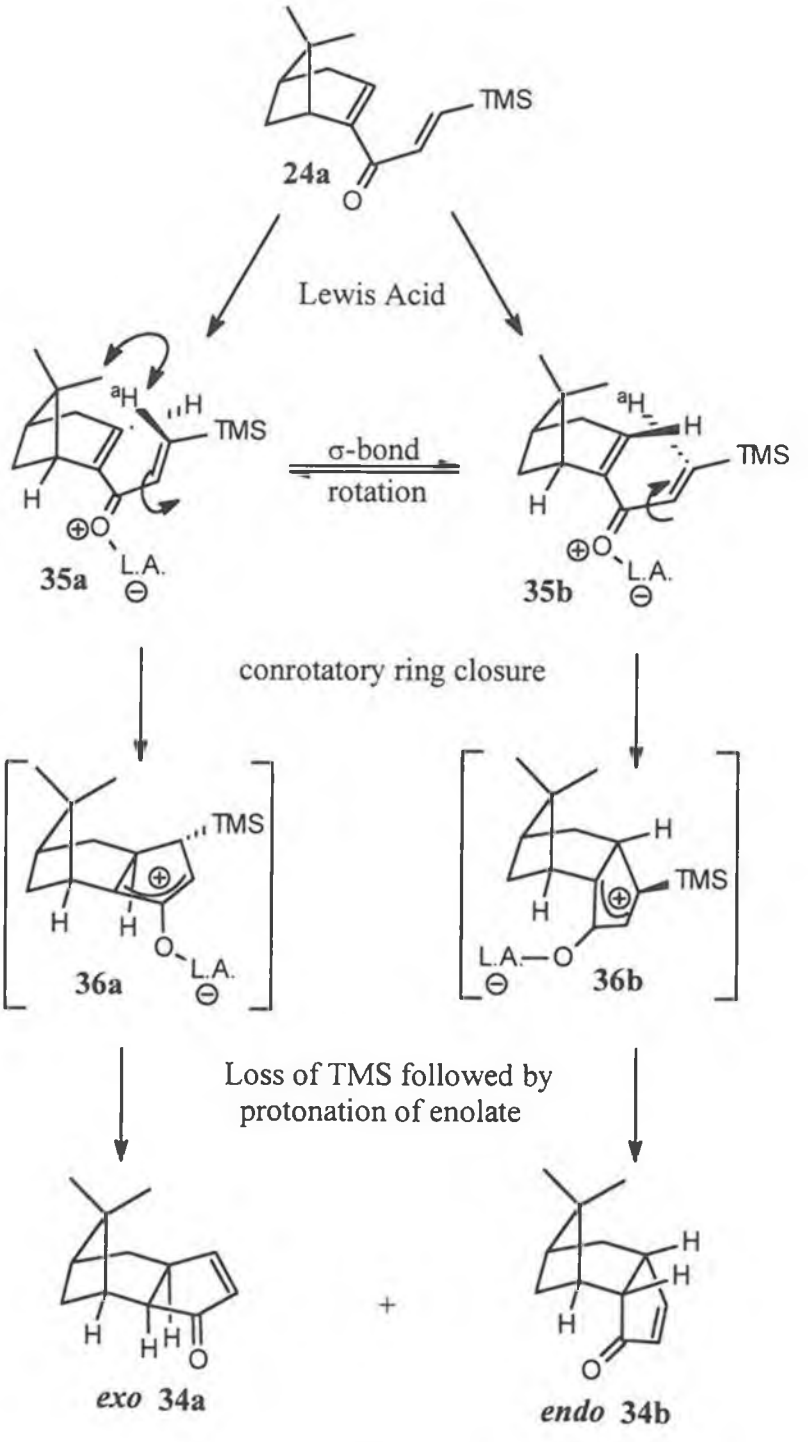
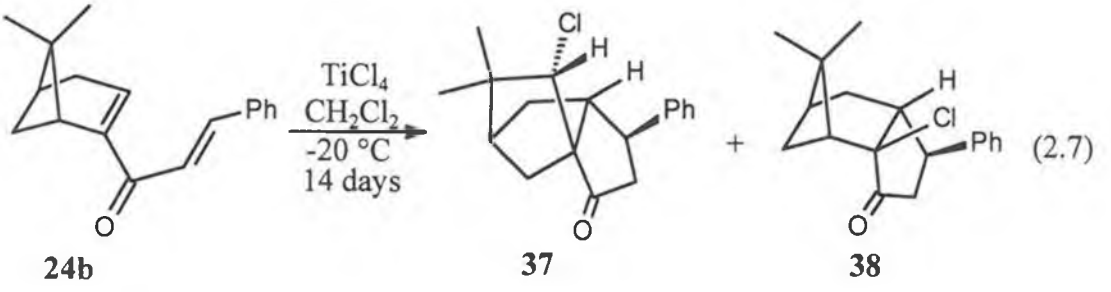



**Figure 2.11.** Steric interactions during cyclization of **24a**.

Myrtenal substrates were also cyclized with $TiCl_4$ to see if chloride trapping would occur, as had been observed in the camphor series. Substrate **24b** was the first to be cyclized (Eq. 2.7). One equivalent of the Lewis Acid was used and the reaction proceeded very slowly at -20 C. After two weeks, starting material was consumed and two products were recovered. Compound **38**, resulting from an *endo* cyclization and subsequent chloride trapping of the oxyallyl carbocation, was formed in 12%. Structural determination of compound **37** proved elusive for some time. $^1$H NMR showed a singlet representing one proton with a chemical shift of 4.25 ppm, and HRMS showed the presence of a chlorine atom. Wagner-Meerwein shifts have been observed in the Nazarov cyclization as discussed in Chapter One. Cyclization of substrate **24b** to form endo intermediate **39**, could then undergo a 1,2-shift to release the strain of the four membered ring, generating intermediate **40** (Figure 2.12). Although the secondary carbocation is less stable than the tertiary carbocation, the strain energy of the four-membered ring may overcome this barrier. This secondary carbocation was trapped by chloride and quenching of the enolate formed compound **37** in 48% yield. It is possible that some *exo* cyclization also occurred, but the orbitals were not properly aligned for the 1,2 shift and the intermediate decomposed. The NOESY determination of a 1,2-shift product will be discussed in detail shortly.




**24b** **37** **38** (2.7)

Substrate **24e** was far more reactive, just as with the disubstituted camphor case (Eq. 2.8). After just ten minutes at -78 °C with one equivalent of $TiCl_4$, starting material was consumed. Again, product resulting from a 1,2 shift was isolated. Compound **42** was isolated in 33% yield and stereochemistry was determined by NOESY and COSY methods. Cyclization occurred in an endo fashion, followed by 1,2-shift and chloride trapping from the back face of the five membered ring. This raises an important point

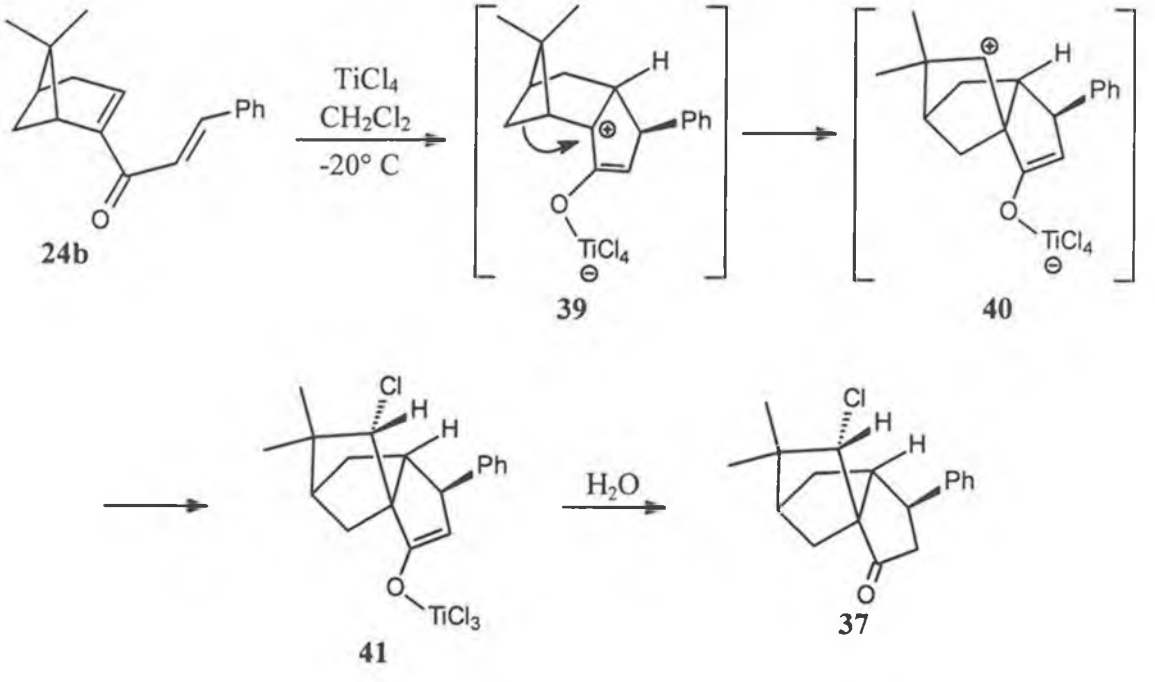
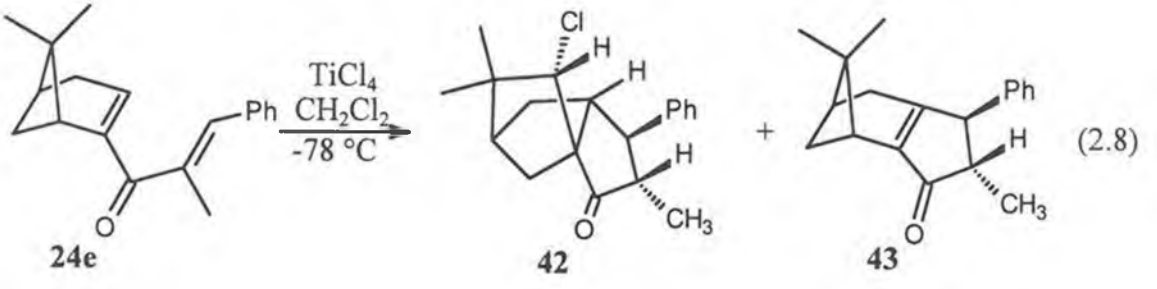



**Figure 2.12.** Wagner-Meerwein shift of substrate **24b**.



about the nature of the transfer of chloride from titanium to the carbocation. In camphor substrates, the carbocation being quenched could receive chloride by an intra- or intermolecular mechanism. However, the apparent stereochemistry of the chlorine in this example precludes internal delivery. The stereochemistry α to the carbonyl was established by approach of a proton to generate the trans stereochemistry between the methyl and phenyl groups. Interactions described in Figure 2.13 and Table 2.7 were used to determine this stereochemistry. COSY methods were used to determine proton conectivities, then NOESY interactions provided evidence for the indicated stereochemistry. $H^c$ showed interactions with both $H^f$ and $H^i$ in support of an *endo* cyclization. Methyl group protons j and k were identified by their interactions with $H^e$ and $H^h$ respectively. Stereochemistry at the chlorinated carbon was determined by interactions of $H^l$ with $H^h$ and protons k. Finally, protons a showed an interaction with $H^c$, indicating a *trans* relationship between protons $H^b$ and $H^c$. The other major product, **43**, presumably results from the normal deprotonation pathway, and was isolated in 29% yield. Stereochemistry is uncertain about the other new chiral centers, but correlation with the previous example suggests that the cyclization occurred in an *endo* fashion and that the phenyl and methyl groups are *trans* to one another.

Substrate **24c**, containing the *Z* olefin geometry, was the next case to be examined (Eq. 2.9). Exposure to one equivalent of $TiCl_4$ at -78 °C proceeded very cleanly to give one product in five minutes. Isolation of this material provided a nearly quantitative yield of isomer **24d** via an apparent Lewis Acid mediated isomerization.

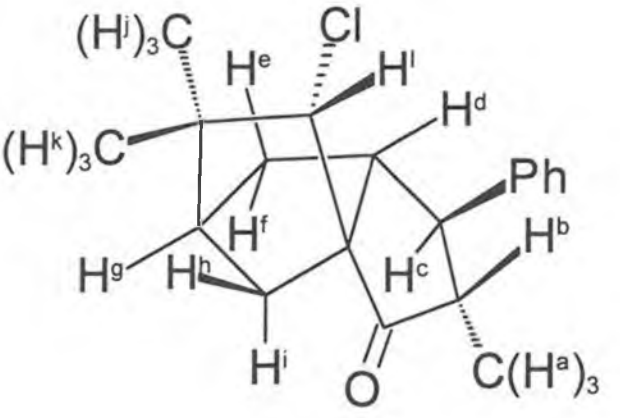
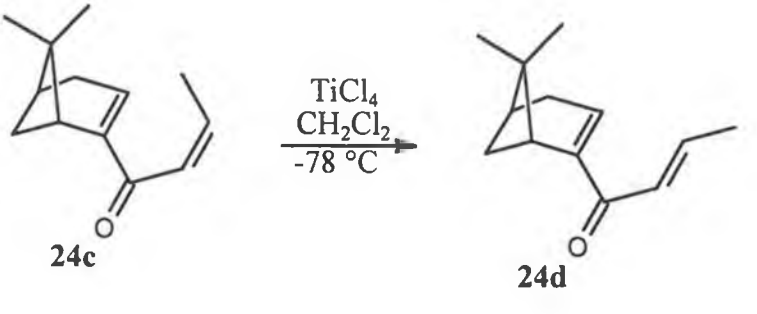



**Figure 2.13.** Structure of compound **42**.

**Table 2.7.** NOESY interactions observed in **42**.

| | | $H^a$ | $H^c$ | $H^d$ | $H^e$ | $H^f$ | $H^g$ | $H^h$ | $H^i$ | $H^j$ | $H^k$ | $H^l$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | δ | 1.03 | 2.52 | 2.81 | 1.98 | 1.45 | 2.10 | 1.83 | 1.74 | 1.13 | 0.96 | 4.27 |
| $H^a$ | 1.03 | | X | | | | | | | | | |
| $H^c$ | 2.52 | X | | | | X | | | X | | | |
| $H^d$ | 2.81 | | | | X | | | | | X | | |
| $H^e$ | 1.98 | | | X | | X | | | | X | | |
| $H^f$ | 1.45 | | X | | X | | X | | | | | |
| $H^g$ | 2.10 | | | | | X | | | X | X | X | |
| $H^h$ | 1.83 | | | | | | | | X | | X | X |
| $H^i$ | 1.74 | | X | | | | X | X | | | | |
| $H^j$ | 1.13 | | | X | X | | X | | | | X | |
| $H^k$ | 0.96 | | | | | | X | X | | X | | X |
| $H^l$ | 4.27 | | | | | | | X | | | X | |




**24c** **24d** (2.9)

Cyclization of the *E* isomer **24d** was not as clean as previous cases. After stirring overnight at -20 °C, several compounds were formed which could not be cleanly isolated. However, $^1$H NMR of the crude mixture showed a singlet around 4.0 ppm similar to the singlet observed in the earlier rearrangement cases.

With several examples of chloride transfer from $TiCl_4$ during the Nazarov cyclization, would other halogens on titanium Lewis Acids transfer in the same fashion? Substrate **14b** was chosen to examine this possibility due to the excellent yields and stereochemistry observed during cyclization with $TiCl_4$. Three other commercially available titanium based Lewis Acids were examined: $TiBr_4$, $TiF_4$ and $TiI_4$. Yields and conditions for these cyclizations were unoptimized.

Substrate **14b** was treated with one equivalent of $TiBr_4$ and stirred at room temperature overnight (Figure 2.14). Two diastereomeric products were isolated in only a 3:1 ratio and in good yield. HRMS indicated that both of these diastereomers were bromide trapped products. More interestingly, selectivity appeared to have been reversed, and the major product now seemed to result from an *endo* cyclization.

To see if this trend would continue as bulkier titanium Lewis Acids were used, $TiI_4$ was also examined. Starting material was consumed after thirteen hours at room temperature in the presence of one equivalent of the Lewis Acid. TLC showed several products and isolation of any pure compound was difficult. One compound was finally isolated in moderate yield, 51%. $^1$H NMR showed one more proton than anticipated, indicating that neither of the expected products, deprotonation forming a cyclopentenone or iodide trapping, had occurred. However, iodide can assist in the removal of $I^+$ in the

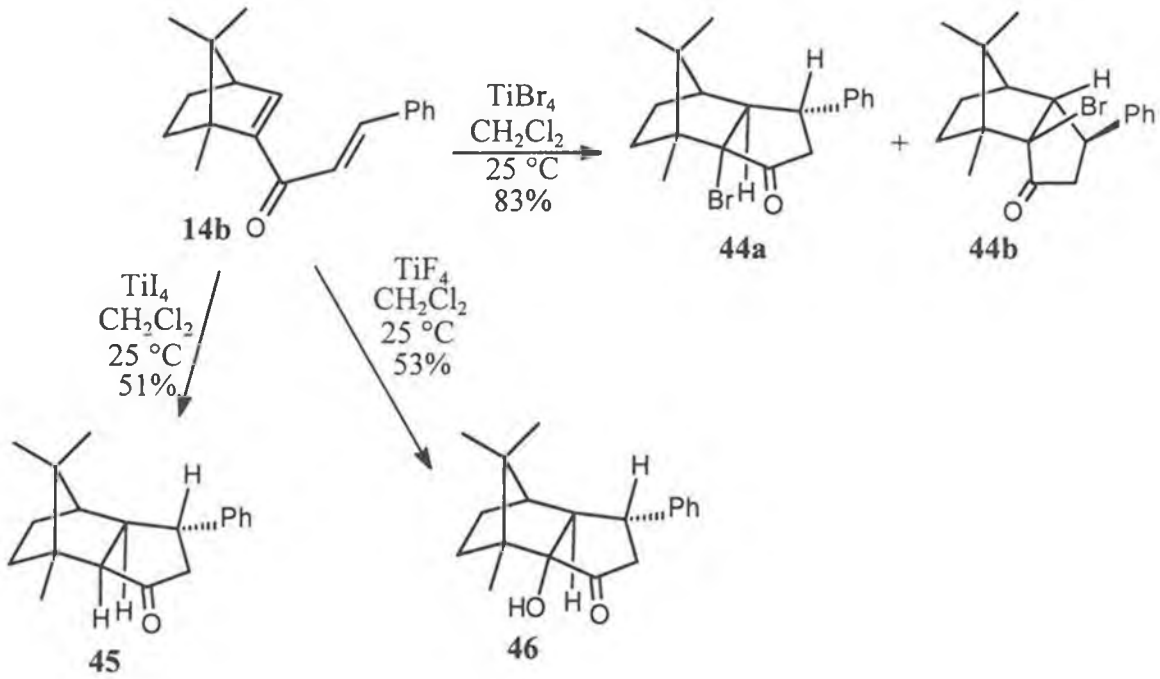



**Figure 2.14.** Cyclization with other titanium Lewis Acids.

presence of protic acid,[16] so it is possible that the iodide trapping product was formed, and then the $I^+$ was removed in the presence of a Lewis Acid, generating the saturated product **45**. Study of the two-dimensional spectra suggested the product resulted from an *exo* cyclization.

Finally, cyclization of **14b** was attempted with $TiF_4$. Two inherent problems with the handling of this Lewis Acid need to be discussed. First, it is very hygroscopic and to add to this problem, the only solvent which $TiF_4$ is soluble in is acetonitrile, which is also hygroscopic. Therefore, the results of this cyclization were not entirely surprising. Alcohol **46** was isolated in 53% yield resulting from trapping of the oxyallyl carbocation by the adventitious water present in the medium.

## Future Work

Several facets of this project require further exploration. Several methods exist for the synthesis of organotitanium reagents.[17] Perhaps these reagents would be able to transfer alkyl groups in much the same way that halogens were transferred here. There are also many other commercially available Lewis Acids, which should be explored. For example, the Lewis Acids originally tried on small scale, $SnCl_4$, $FeCl_3$ and $BF_3 \cdot OEt_2$, should be examined. $Al(CH_3)_3$ and $Sn(CH_3)_4$ may also be viable sources of alkyl groups, which could be transferred during the cyclization. Finally, the synthesis of a bicyclo[2.2.2]octane system and the torquoselectivity of its cyclization should be studied.

## Conclusion

Despite several unexpected results (chloride trapping and Wagner-Meerwein shifts) torquoselectivity was observed in all examples in poor to excellent ratios. The facial bias of these bicyclic systems was enough to favor one cyclization over the other. The bridgehead methyl group in camphor was the key aspect in determining the torquoselectivity, while the less influential gem dimethyl group in myrtenal led to a slight selectivity. Myrtenal also displayed the opposite selectivity because the carbonyl was not close enough to interact; instead interactions with the vinyl proton led to *endo* selectivity. Also, preliminary studies on the trapping of other nucleophiles from titanium Lewis Acids proved successful. The usefulness of these trapped and rearranged products may be numerous and will be explored by others in the future.

## Experimental Section

**General.** Reactions were conducted in oven-dried (120 °C) or flame-dried glassware under an inert nitrogen atmosphere unless otherwise stated. Transfer of anhydrous solvents or mixtures was accomplished via oven-dried syringes or cannula. Solvents were distilled before use: dichloromethane from calcium hydride; diethyl ether and tetrahydrofuran from sodium benzophenone ketyl and toluene and benzene from sodium. Reagents purchased from commercial vendors were used without purification unless stated otherwise. Thin layer chromatography (TLC) was performed on glass plates precoated with 0.25mm Kieselgel 60 $F_{254}$ (Merck or Whatman). Flash columns were packed with 230-400 mesh silica gel (Merck or Baxter). Radial chromatography was performed on glass rotors precoated with 1, 2 or 4 mm of silica gel 60 $PF_{254}$ containing gypsum. Melting points were obtained on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected.

Proton nuclear magnetic resonance spectra ($^1$H NMR) were recorded on a 300 or 500 MHz Varian NMR and the chemical shifts are reported on the δ scale (ppm) downfield from tetramethylsilane. Coupling constants (*J*) are reported in Hz. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets, etc. Carbon nuclear magnetic resonance spectra ($^{13}$C NMR) were obtained at 75 MHz or 125 MHz and are reported (ppm) relative to the centerline of a triplet at 77.23 for deuterochloroform. Nuclear Overhauser Effect Spectroscopy (NOESY) spectra and Correlated Spectroscopy (COSY) spectra were obtained on a 500 MHz Varian NMR.

Infrared (IR) spectra were measured with a Mattson FT-IR infrared spectrophotometer. Mass spectra were determined on a VG Micromass 7050E mass spectrometer equipped with a VG 2000 Data system.

## Synthesis of Dienols

**General Procedure.** The hydrazone (3.0 mmol) was dissolved in THF (18 mL) and cooled to -78 °C. *sec*-Butyllithium (6.0 mL of a 1.1 M solution in cyclohexane, 6.6 mmol) was added to the reaction via syringe, turning the solution very dark red. After stirring at -78 °C for 1.5 hours, the reaction was warmed to 0 °C resulting in evolution of nitrogen and color change to a light yellow. Once nitrogen evolution had ceased (~35 min), the reaction was cooled once again to -78 °C and the aldehyde (3.6 mmol) was added slowly via syringe. After about 10 min the reaction was quenched with aqueous $NH_4Cl$ (10 mL) and separated. The aqueous layer was washed with 2 x 25 mL portions of $Et_2O$. The combined organic layers were dried with $MgSO_4$, filtered and concentrated yielding a yellow oil. Purification was achieved via flash column chromatography (silica gel, 3 x 20 cm column).

**Dienol 13a.** α,β-unsaturated aldehyde **12a** (147 mg, 1.15 mmol) was added via syringe to the vinyl anion of camphor (1.49 mmol) prepared according to the above procedure. Flash column chromatography (silica gel, 2 x 20 cm column, hexanes/EtOAc 9:1) of the residue yielded **13a** as a pale yellow oil (133 mg, .503 mmol, 44%): one diastereomer, $R_f$ 0.20 (hexanes/EtOAc 9:1); IR (neat) 3375, 2951, 2871 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.13-5.92 (m, 2H), 5.84-5.80 (m, 1H), 4.67 (br s, 1H), 2.29 (dd, 1H,

$J$ = 3.6, 3.6 Hz), 1.88-1.79 (m, 1H), 1.59-1.46 (m, 2H), 1.04 (s, 3H), 1.18-0.97 (m, 2H), 0.78 (s, 3H), 0.76 (s, 3H), 0.08 (s, 9H).

**Dienol 13d.** The α, β-unsaturated aldehyde **12d**[8] (400 mg, 3.57 mmol) was added via syringe to the vinyl anion of camphor (3.00 mmol) prepared according to the above procedure. Flash column chromatography (silica gel, 3 x 15 column, hexanes/EtOAc 19:1) of the residue yielded **13d** as a colorless oil (359 mg, 1.45 mmol, 50%): one diastereomer $R_f$ 0.16 (hexanes/EtOAc 9:1); IR (neat) 3553, 2957, 2871 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$), δ 5.84 (br s, 1H), 5.73 (d, 1H, $J$ = 15.6 Hz), 5.27 (dd, 1H, $J$ = 15.6, 7.5 Hz), 4.64 (br s, 1H), 2.29 (dd, 1H, $J$ = 3.6, 3.6 Hz), 1.89-1.79 (m, 1H), 1.58-1.40 (m, 2H), 1.03 (s, 9H), 1.04-0.96 (m, 2H), 0.81 (s, 3H), 0.78 (s, 3H), 0.76 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 150.7, 143.6, 128.4, 126.4, 71.7, 57.4, 54.1, 51.4, 33.1, 32.5, 32.0, 25.7, 19.8, 19.7, 12.1.

**Dienol 13e.** α-Methyl-*trans*-cinnamaldehyde (339 mg, 2.32 mmol) was added via syringe to the vinyl anion of camphor (1.94 mmol) prepared according to the above procedure. Flash column chromatography (silica gel, 3 x 15 cm column, hexanes/EtOAc 19:1) of the residue yielded **13e** as a pale yellow oil (431 mg, 1.55 mmol, 80%): one diastereomer, $R_f$ 0.14 (hexanes/EtOAc 9:1); IR (neat) 3393, 3054, 2953, 2872 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.38-7.20 (m, 5H), 6.63 (s, 1H), 5.96 (d, 1H, $J$ = 3.0 Hz), 4.78 (s, 1H), 2.35 (dd, 1H, $J$ = 3.0, 3.0 Hz), 1.92-1.84 (m, 1H), 1.74 (s, 3H), 1.68-1.62 (m, 1H), 1.53-1.46 (m, 1H), 1.10 (s, 3H), 1.04-0.91 (m, 2H), 0.85 (s, 3H), 0.79 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$); δ 148.7, 138.3, 137.9, 129.9, 129.1, 128.3, 126.9, 126.7, 75.5, 57.6, 54.3, 51.5, 31.3, 25.8, 19.8, 19.7, 13.5, 11.7.

**Hydrazone 22.** Nopinone **2** (2.00 g, 14.5 mmol) and trisyl hydrazide **10** (5.18g, 17.4mmol) were suspended in acetonitrile (30 mL). Concentrated HCl (1.4 mL) was then added to the reaction and it was allowed to stir overnight. Excess hydrazide was removed by filtration. The filtrate was then placed in a separatory funnel and diluted with water (50 mL). As the layers began to separate crystals formed in the acetonitrile layer. The remaining aqueous layer was diluted with 50 mL of saturated NaCl solution and washed with 2 x 35 mL portions of acetonitrile. Prolonged cooling of the combined organics (-20 °C for two days) allowed the hydrazone to crystallize. Filtration and washing with fresh acetonitrile yielded **22** as white crystals (1.98 g, 4.73 mmol, 33%): mp 168-169 °C, $R_f$ 0.14 (hexanes/EtOAc 9:1); IR (KBr) 3238, 2958, 1387, 1166 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.16 (br s, 1H), 7.15 (s, 2H), 4.24 (sept, 2H, $J$ = 6.6 Hz), 2.90 (sept, 1H, $J$ = 6.6 Hz), 2.57 (dd, 1H, $J$ = 6.3, 6.3 Hz), 2.47-2.38 (m, 1H), 2.37-2.21 (m, 2H), 2.09-1.82 (m, 4H), 1.30-1.24 (m, 18H), 1.22 (s, 3H), 0.60 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 153.2, 151.5, 131.6, 123.9, 51.3, 40.7, 40.4, 34.3, 30.1, 27.5, 25.7, 25.1, 25.0, 23.8, 22.3, 22.1, 20.0. Anal. calcd for $C_{24}H_{38}N_2SO_2$: C, 68.86; H 9.15. Found: C, 68.75; H, 9.08.

**Dienol 23a.** (2-Bromovinyl)-*E*-rimethylsilane (1.19g, 6.66 mmol) was added very slowly via syringe to a flask of Mg powder (202 mg, 8.33 mmol) suspended in THF (4 mL) fitted with a reflux condenser. The flask was cooled with ice as necessary. Once the Grignard reagent was prepared in this fashion, the mixture was cooled to 0 °C and myrtenal (500 mg, 3.33 mmol) was added slowly via syringe. After 10 minutes the reaction was quenched with saturated $NH_4Cl$ (5 mL) and stirred overnight. The phases were separated and the aqueous layer washed with 2 x 15 mL of $Et_2O$. The organic layers were combined, dried with $MgSO_4$, filtered and concentrated to give a pale yellow

oil. Flash column chromatography (silica gel, 3 x 20 cm column, hexanes/EtOAc 9:1) yielded **23a** as a very pale yellow oil (680 mg, 2.72 mmol, 82%): one diastereomer, $R_f$ 0.21 (hexanes/EtOAc 9:1); IR (neat) 3521, 3091 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.93-5.89 (m, 2H), 5.54-5.46 (m, 1H), 4.55 (br s, 1H), 2.44-2.04 (m, 5H), 1.61-1.57 (m, 1H), 1.26 (s, 3H), 1.17 (d, 1H, $J$ = 8.4 Hz), 0.77 (s, 3H), 0.06 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 148.7, 145.8, 129.7, 119.3, 66.0, 41.7, 41.1, 38.0, 31.9, 31.5, 26.3, 21.6, -1.08.

**Dienol 23b.** Cinnamaldehyde (393 mg, 2.97 mmol) was added via syringe to the vinyl anion derived from nopinone (2.47 mmol) prepared according to the above procedure. Flash column chromatography (silica gel, 3 x 20 cm column, hexanes/EtOAc 19:1) could not completely purify the dienol, so the crude yellow oil (526 mg, 1.96 mmol, 79%) was oxidized in the next step without further purification: $R_f$ 0.13 (hexanes/EtOAc 9:1); $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.62 (dd, 1H, $J$ = 15.9, 5.7 Hz), 6.15 (dd, 1H, $J$ = 15.9, 6.3 Hz), 5.62-5.58 (m, 1H), 4.72 (br s, 1H), 2.46-2.39 (m, 1H), 2.35-2.24 (m, 3H), 2.16-2.09 (m, 1H), 1.69 (br s, 1H), 1.29 (s, 3H), 1.21 (dd, 1H, $J$ = 8.4, 6.6 Hz), 0.87 (s, 3H).

**Dienol 23c.** 1-Propenylmagnesium bromide (27 mL of a 0.50 M solution in THF, 13 mmol) was added slowly via syringe to a 0 °C solution of myrtenal (1.0g, 6.7 mmol) in THF (7 mL). After 5 minutes the reaction was quenched by addition of saturated $NH_4Cl$ (10 mL) and diluted with water (10 mL). The phases were separated and the aqueous phase was washed with 2 x 25 mL portions of $Et_2O$. The combined organics were dried with $MgSO_4$, filtered and concentrated. Flash column chromatography (silica gel, 4 x 15 cm column, Hexanes/EtOAc 19:1) yielded **23c** as a pale yellow oil (1.0 g, 5.3

mmol, 80%). The alcohol was a crude mixture of four diastereomers and was taken on directly to the oxidation.

**Dienol 23e.** α-Methyl-*trans*-cinnamaldehyde (459 mg, 3.14 mmol) was added via syringe to the vinyl anion of nopinone (2.62 mmol) prepared according to the above procedure. Flash column chromatography (silica gel, 3 x15 cm column, Hexanes/EtOAc 19:1) of the residue yielded **23e** as a pale yellow oil (635 mg, 2.25 mmol, 85%): one diastereomer, $R_f$ 0.12 (Hexanes/EtOAc 9:1); IR (neat) 3383, 2983, 2918, 2830 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.43-7.20 (m, 5H), 6.60 (s, 1H), 5.63 (m, 1H), 4.53 (s, 1H), 2.46-2.11 (m, 5H), 1.90-1.82 (m, 1H), 1.82 (s, 3H), 1.29 (s, 3H), 1.17 (d, 1H, $J$ = 5.7 Hz), 0.84 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 148.1, 138.0, 129.8, 129.2, 128.3, 126.6, 126.4, 118.6, 80.3, 42.4, 41.2, 38.1, 32.1, 31.5, 26.4, 21.4, 14.8.

## Oxidation of Dienols

**General Procedure.** To a solution of dienol (1.70 mmol) dissolved in $CH_2Cl_2$ (100 mL) $BaMnO_4$ (17.0 mmol) was added and allowed to stir overnight. Excess solvent was removed under reduced pressure until a thick sludge remained. This material was plugged through Celite with EtOAc and concentrated to give a light yellow oil. Purification was achieved via flash column chromatography (silica gel, 3 x 20 cm column) or radial chromatography (4 mm plate).

**Dienone 14a.** Reaction of dienol **13a** (133 mg, 0.503 mmol) and $BaMnO_4$ (1.29 g, 5.03 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4 mm plate, hexanes/EtOAc 9:1) yielded **14a** as a colorless oil (100 mg, 0.381 mmol, 76%): $R_f$ 0.49 (hexanes/EtOAc 9:1); IR (neat) 2875, 2852, 1650 $cm^{-1}$; $^1H$ NMR

(500 MHz, $CDCl_3$) δ 7.06 (d, 1H, $J$ = 18.5 Hz), 6.89 (d, 1H, $J$ = 7.0 Hz), 6.87 (d, 1H, $J$ = 8.0 Hz), 2.51 (dd, 1H, $J$ = 4.0, 4.0 Hz), 1.94 (ddd, 1H, $J$ = 16.0, 8.5, 3.5 Hz), 1.61 (ddd, 1H, $J$ = 12.5, 8.5, 4.0 Hz), 1.27 (s, 3H), 1.16 (ddd, 1H, $J$ = 12.5, 8.5, 4.0 Hz), 0.98 (ddd, 1H, $J$ = 12.5, 8.5, 3.5 Hz), 0.82 (s, 3H), 0.81 (s, 3H), 0.14 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 188.7, 149.9, 148.1, 145.6, 139.5, 56.2, 54.6, 52.8, 31.2, 25.3, 19.7, 19.1, 11.8, -1.5. Anal. calcd for $C_{16}H_{26}OSi$: C, 73.22; H, 9.98. Found: C, 73.00; H, 9.96.

**Dienone 14b.** Reaction of dienol **13b** (495 mg, 1.85 mmol) and $BaMnO_4$ (4.74 g, 18.5 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4 mm plate, hexanes/EtOAc 19:1) yielded **14b** as a yellow oil (372 mg, 1.40 mmol, 76%): $R_f$ 0.64 (hexanes/EtOAc 9:1); IR (neat) 2952, 1655, 1572 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl3) δ 7.58-7.55 (m, 3H), 7.40-7.33 (m, 3H), 7.13 (d, 1H, $J$ = 16.0 Hz), 6.95 (d, 1H, $J$ = 3.5 Hz), 2.54 (dd, 1H, $J$ = 3.5, 3.5 Hz), 1.97 (ddd, 1H, $J$ = 16.0, 8.5, 3.5 Hz), 1.64 (ddd, 1H, $J$ = 12.0, 8.5, 3.5 Hz), 1.31 (s, 3H), 1.22 (ddd, 1H, $J$ = 12.5, 9.0, 3.5 Hz), 1.01 (ddd, 1H, $J$ = 12.5, 9.0, 3.5 Hz), 0.85 (s, 3H), 0.83 (s, 3H); $^{13}$C NMR (125 MHz, CDCl3) δ 189.3, 150.7, 147.3, 141.8, 135.4, 130.2, 129.0, 128.4, 124.1, 56.3, 54.8, 52.8, 31.2, 25.3, 19.7, 19.2, 11.9. Anal. calcd for $C_{19}H_{22}O$: C, 85.70; H, 8.32. Found: C, 85.43; H, 8.43.

**Dienone 14c.** Reaction of dienol **13c** (429 mg, 2.08 mmol) and $BaMnO_4$ (5.33 g, 20.8 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4 mm plate, hexanes/EtOAc 19:1) yielded **14c** as a pale yellow oil (340 mg, 1.66 mmol, 80%): $R_f$ 0.37 (hexanes/EtOAc 9:1); IR (neat) 2877, 1663, 1617 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 6.82 (dq, 1H, $J$ = 15.0, 6.5 Hz), 6.78 (d, 1H, $J$ = 3.5 Hz), 6.48 (d, 1H, $J$ = 15.0 Hz), 2.48 (dd, 1H, $J$ = 3.5, 3.5 Hz), 1.92 (ddd, 1H, $J$ = 16.5, 9.0, 3.5 Hz),

1.88 (d, 1H, $J$ = 7.0 Hz), 1.59 (ddd, 1H, $J$ = 12.5, 9.0, 3.5 Hz), 1.16 (ddd, 1H, $J$ = 12.5, 9.0, 4.0 Hz), 0.96 (ddd, 1H, $J$ = 12.0, 9.0, 3.5 Hz), 1.25 (s, 3H), 0.79 (s, 3H), 0.78 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 189.8, 150.1, 146.9, 141.5, 129.4, 56.2, 54.6, 52.7, 31.2, 25.3, 19.7, 19.1, 18.4, 11.8.

**Dienone 14d.** Reaction of dienol **13d** (334 mg, 1.34 mmol) and $BaMnO_4$ (3.45 g, 13.4 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4mm plate, hexanes/EtOAc 99:1 ramped to hexanes/EtOAc 19:1) yielded **14d** as a colorless oil (291 mg, 1.18 mmol, 88%): $R_f$ 0.29 (hexanes/EtOAc 9:1); IR (neat) 2989, 2872, 1661, 1614 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 6.83 (d, 1H, $J$ = 15.6 Hz), 6.82 (d, 1H, $J$ = 3.6 Hz), 6.37 (d, 1H, $J$ = 15.6 Hz), 2.50 (dd, 1H, $J$ = 3.9, 3.9 Hz), 1.94 (ddd, 1H, $J$ = 15.9, 8.4, 3.9 Hz), 1.61 (ddd, 1H, $J$ = 12.0, 9.0, 3.6 Hz), 1.28 (s, 3H), 1.18 (ddd, 1H, $J$ = 12.3, 9.0, 3.6 Hz), 1.10 (s, 9H), 0.98 (ddd, 1H, $J$ = 12.3, 9.3, 3.6 Hz), 0.82 (s, 3H), 0.81 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 190.2, 156.3, 150.3, 147.0, 122.4, 56.2, 54.6, 52.6, 33.9, 31.2, 29.0, 25.3, 19.7, 19.1, 11.9. Anal. calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.20; H, 10.72.

**Dienone 14e.** Reaction of dienol **13e** (403 mg, 1.43 mmol) and $BaMnO_4$ (3.66 g, 14.3 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4 mm plate, hexanes/EtOAc 99:1 ramped to hexanes/EtOAc 19:1) yielded **14e** as a pale yellow oil (351 mg, 1.25 mmol, 88%): $R_f$ 0.38 (hexanes/EtOAc 9:1); IR (neat) 2941, 1626, 1575 cm$^{-1}$; $^1$H NMR (300 MHz, $CDCl_3$) δ 7.44-7.30 (m, 6H), 6.52 (d, 1H, $J$ = 3.6 Hz), 2.54 (dd, 1H, $J$ = 3.6, 3.6 Hz), 2.11 (s, 3H), 1.96 (ddd, 1H, $J$ = 16.2, 8.4, 3.6 Hz), 1.64 (ddd, 1H, $J$ = 12.0, 8.4, 3.6 Hz), 1.33 (ddd, 1H, $J$ = 12.0, 8.4, 3.6 Hz), 1.24 (s, 3H), 1.02 (ddd, 1H, $J$ = 12.0, 9.0, 3.6 Hz), 0.95 (s, 3H), 0.85 (s, 3H); $^{13}$C NMR (75 MHz,

$CDCl_3$) δ 197.0, 148.9, 146.3, 139.9, 138.6, 136.4, 129.9, 128.6, 128.4, 55.9, 55.3, 53.0, 31.3, 25.7, 19.9, 19.2, 14.0, 11.4. Anal. calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.38; H, 8.60.

**Dienone 24a.** Reaction of dienol **23a** (0.68g, 2.7 mmol) and $BaMnO_4$ (4.9 g, 19 mmol) according to the above procedure and radial chromatography (silica gel, 4mm plate, hexanes/EtOAc 19:1) yielded **24a** as a white solid (480 mg, 1.9 mmol, 70%): mp 59-60 °C; $R_f$ 0.43 (hexanes/EtOAc 9:1); IR (KBr) 2954, 1645, 1611 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.13-7.03 (m, 2H), 6.82-6.79 (m, 1H), 2.98 (ddd, 1H, $J$ = 3.3, 3.3, 1.0 Hz), 2.53 (dd, 1H, $J$ = 2.1, 2.1 Hz), 2.49-2.44 (m, 2H), 2.17-2.12 (m, 1H), 1.33 (s, 3H), 1.07 (d, 1H, $J$ = 5.4 Hz), 0.76 (s, 3H), 0.15 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 188.5, 149.9, 146.5, 137.9, 137.2, 40.5, 40.3, 37.7, 32.9, 31.4, 26.1, 21.1, -1.5. Anal. calcd for $C_{15}H_{24}OSi$: C, 72.54; H, 9.73. Found: C, 72.70; H, 9.79.

**Dienone 24b.** Reaction of dienol **23b** (498 mg, 1.96 mmol) and $BaMnO_4$ (5.02 g, 19.6 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4mm plate, hexanes/EtOAc 19:1) yielded **24b** as a pale yellow oil (270 mg, 1.06 mmol, 56%): $R_f$ 0.56 (hexanes/EtOAc 9:1); IR (neat) 3060, 2973, 1651, 1601 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.62-7.54 (m, 3H), 7.43-7.34 (m, 4H), 6.91-6.88 (m, 1H), 3.07 (dd, 1H, $J$ = 5.7, 5.7 Hz), 2.57-2.49 (m, 2H), 2.21-2.15 (m, 1H), 1.37 (s, 3H), 1.12 (d, 1H, $J$ = 9.3 Hz), 0.93-0.87 (m, 1H), 0.80 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 188.8, 150.6, 142.6, 137.2, 135.4, 130.2, 129.0, 128.4, 121.5, 40.5, 40.4, 37.7, 32.9, 31.4, 26.1, 21.2.

**Dienones 24c-d.** Reaction of dienol **23c** (1.02 g, 5.30 mmol) and $BaMnO_4$ (13.6 g, 53.0 mmol) according to the above procedure and medium pressure liquid

chromatography (silica gel, 2.5 x 26.5 cm, hexanes/EtOAc 19:1) yielded **24c** (419mg, 2.20 mmol, 41%) **24d** (420 mg, 2.21 mmol, 41%).

**24c:** pale yellow oil; $R_f$ 0.42 (Hexanes/EtOAc 9:1); IR (neat) 2918, 1654, 1612 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 6.74-6.71 (m, 1H), 6.54 (dq, 1H, $J$ = 11.7, 1.8 Hz), 6.21 (dq, 1H, $J$ = 11.7, 7.2 Hz), 2.99 (ddd, 1H, $J$ = 5.7, 5.7, 1.5 Hz), 2.58-2.40 (m, 2H), 2.17-2.10 (m, 2H), 2.05 (br dd, 3H, $J$ = 7.2, 1.5 Hz), 1.34 (s, 3H), 1.06 (d, 1H, $J$ = 10.0 Hz), 0.76 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 191.4, 150.8, 141.1, 137.0, 125.0, 40.5, 39.7, 37.6, 32.8, 31.4, 26.1, 21.1, 16.1.

**24d:** pale yellow oil; $R_f$ 0.33 (hexanes/EtOAc 9:1); IR (neat) 2917, 1662, 1617 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.87 (dq, 1H, $J$ = 15.5, 7.0 Hz), 6.74-6.72 (m, 1H), 6.67 (dq, 1H, $J$ = 15.5, 1.5 Hz), 2.97 (ddd, 1H, $J$ = 5.5, 5.5, 1.5 Hz), 2.55-2.41 (m, 3H), 2.15-2.11 (m, 1H), 1.91 (dd, 3H, $J$ = 7.0, 1.5 Hz), 1.33 (s, 3H), 1.05 (d, 1H, $J$ = 9.0 Hz), 0.75 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 189.1, 149.9, 142.2, 136.9, 126.6, 40.4, 40.2, 37.6, 32.8, 31.1, 26.0, 21.1, 18.6.

**Isomerization of 24c to 24d.** $TiCl_4$ (70 μL of a 3.70 M solution in $CH_2Cl_2$, 0.26 mmol) was added to a -78 °C solution of dienone **24c** (49 mg, 0.26 mmol) dissolved in 26 mL of $CH_2Cl_2$. After 5 minutes starting material had been consumed and the reaction was quenched with water (20 mL) and allowed to warm to room temperature. The phases were separated and the aqueous phase was washed with 2 x 20 mL portions of $Et_2O$. The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Radial chromatography (silica gel, 2mm plate, hexanes/EtOAc 19:1) yielded a pale yellow oil (45 mg, 0.24 mmol, 91%) whose spectral data were identical to those of **24d**.

**Dienone 24e.** Reaction of dienol **23e** (479 mg, 1.70 mmol) and $BaMnO_4$ (4.36 g, 17.0 mmol) according to the above procedure and radial chromatography of the residue (silica gel, 4 mm plate, hexanes/EtOAc 19:1) yielded **24e** as a very pale yellow oil (394 mg, 1.40 mmol, 83%): $R_f$ 0.37 (hexanes/EtOAc 9:1); IR (neat) 2920, 1630 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.43-740 (m, 4H), 7.37-7.31 (m, 1H), 7.16 (br s, 1H), 6.49-6.47 (m, 1H), 2.86 (dd, 1H, $J$ = 5.7, 5.7 Hz), 2.60-2.47 (m, 3H), 2.20-2.15 (m, 1H), 2.14 (s, 3H), 1.38 (s, 3H), 1.21 (d, 1H, $J$ = 8.7 Hz), 0.88 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 198.6, 148.6, 138.4, 137.1, 136.9, 136.3, 129.7, 128.6, 128.3, 42.2, 40.5, 37.9, 32.7, 31.6, 26.1, 21.2, 14.9. Anal. calcd for $C_{19}H_{22}O$: C, 85.67; H, 8.32. Found: C, 85.58; H, 8.38.

## Cyclization of Dienones

**Tricyclic ketones 28.** $BF_3 \cdot OEt_2$ (94 μL, 0.76 mmol) was added to a -78 °C solution of dienone **14a** (50 mg, 0.19 mmol) dissolved in 19 mL of $CH_2Cl_2$. After stirring for ten minutes the reaction was warmed to 0 °C and allowed to stir overnight. Water (10 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 15 mL portions of $Et_2O$ and the organic layers were combined. These combined layers were dried with $MgSO_4$, filtered and concentrated to give a colorless oil. Radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 9:1) yielded **28a** and **28b** as a 10:1 ratio of diastereomers (25 mg, 0.14 mmol, 75%).

**28a**: clear colorless oil; $R_f$ 0.37 (hexanes/EtOAc 9:1); IR (neat) 2955, 1745 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.74 (dd, 1H, $J$ = 5.5, 3.0 Hz), 6.11 (dd, 1H, $J$ = 5.5, 2.5 Hz), 2.80 (ddd, 1H, $J$ = 5.5, 3.0, 3.0 Hz), 2.13 (d, 1H, $J$ = 6.0 Hz), 1.97 (d, 1H, $J$ = 4.5 Hz), 1.86 (ddd, 1H, $J$ = 16.5, 12.5, 4.0 Hz), 1.59 (ddd, 1H, $J$ = 16.0, 12.5, 4.0 Hz), 1.29

(ddd, 1H, $J$ = 13.5, 9.5, 4.0 Hz), 1.19 (ddd, 1H, $J$ = 12.5, 9.5, 4.0 Hz), 1.15 (s, 3H), 0.78 (s, 3H), 0.72 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 212.6, 167.9, 137.0, 58.7, 53.4, 52.0, 48.4, 48.2, 38.3, 29.6, 23.2, 21.6, 12.2. HRMS (EI) calcd for $C_{13}H_{18}O$ m/e 190.1358, found m/e 190.1383.

**28b**: clear colorless oil; $R_f$ 0.34 (hexanes/EtOAc 9:1); IR (neat) 2871, 1699 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.55 (dd, 1H, $J$ = 5.5, 2.5 Hz), 6.80 (dd, 1H, $J$ = 5.5, 2.5 Hz), 3.39 (ddd, 1H, $J$ = 7.0, 5.5, 2.5 Hz), 2.45 (dd, 1H, $J$ = 6.5, 2.5 Hz), 1.93 (dd, 1H, $J$ = 4.5, 4.5 Hz), 1.64-1.57 (m, 1H), 1.41-1.34 (m, 1H), 1.27-1.21 (m, 1H), 1.06 (s, 3H), 1.02 (s, 3H), 0.91 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 211.5, 166.5, 135.3, 56.6, 53.5, 51.1, 49.2, 47.6, 31.0, 23.6, 20.1, 18.7, 15.5.

**Tricyclic ketone 31a.** $TiCl_4$ (43 μL of a 3.70 M solution in $CH_2Cl_2$, 0.16 mmol) was added to a -78 °C solution of dienone **14a** (42 mg, 0.16 mmol) dissolved in 16 mL of $CH_2Cl_2$. After stirring for 30 minutes the reaction was warmed to 0 °C and stirred for one hour. Water (15 mL) was added to quench the reaction and the phases were separated. The aqueous layer was washed with 2 x 25 mL portions of $Et_2O$ and the organic layers were combined. These combined organics were dried with $MgSO_4$, filtered and concentrated to give a pale yellow oil. Radial chromatography (silica gel, 2mm plate, hexanes/EtOAc 19:1) yielded **28a** and **28b** as a 6:1 ratio of diastereomers (13 mg, 0.068 mmol, 43%) and **31a** (15 mg, 0.050 mmol, 31%).

**31a**: white solid, mp 81-83 °C; $R_f$ 0.52 (hexanes/EtOAc 9:1); IR (KBr) 2954, 1735 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 2.53 (dd, 1H, $J$ = 18.5, 12.5 Hz), 2.33 (dd, 1H, $J$ = 18.5, 9.0 Hz), 2.15 (ddd, 1H, $J$ = 14.0, 9.5, 4.5 Hz), 2.04 (d, 1H, $J$ = 8.0 Hz), 1.85-1.78 (m, 1H), 1.62 (d, 1H, $J$ = 4.0 Hz), 1.37 (ddd, 1H, $J$ = 13.5, 12.0, 4.5 Hz), 1.27-1.20

(m, 1H), 1.13 (s, 3H), 1.17-1.09 (m, 1H), 0.90 (s, 3H), 0.81 (s, 3H), 0.05 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 213.5, 80.1, 57.7, 55.4, 51.5, 48.6, 37.5, 32.5, 29.1, 24.1, 23.0, 22.8, 9.8, -3.4. HRMS (EI) calcd for $C_{16}H_{27}OClSi$ m/e 298.1520, found m/e 298.1530.

**28a** and **28b**: all data was consistent with the *exo* and *endo* products generated with $BF_3 \cdot OEt_2$.

**Tricyclic ketone 31b.** $TiCl_4$ (63 μL of a 3.70 M solution in $CH_2Cl_2$, 0.23 mmol) was added to a -78 °C solution of dienone **14b** (62 mg, 0.23 mmol) dissolved in 23 mL of $CH_2Cl_2$. After stirring for 30 minutes the reaction was warmed to 0 °C and stirred for 5 hours. Water (15 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 15 mL portions of $Et_2O$ and the organic layers were combined. These combined layers were dried with $MgSO_4$, filtered and concentrated to give a pale yellow oil. Radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 97:3) yielded **31b** as a white solid (60 mg, 0.20 mmol, 87%): mp 103-104 °C; $R_f$ 0.33 (hexanes/EtOAc 9:1); IR (KBr) 2959, 2893, 1735 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 3.23 (ddd, 1H, $J$ = 10.8, 8.4, 6.6 Hz), 3.00 (dd, 1H, $J$ = 18.0, 10.8 Hz), 2.81 (dd, 1H, $J$ = 18.0, 8.4 Hz), 2.38 (d, 1H, $J$ = 6.6 Hz), 2.18 (ddd, 1H, $J$ = 13.5, 9.3, 4.5 Hz), 1.19 (d, 1H, $J$ = 4.5 Hz), 1.81 (ddd, 1H, $J$ = 15.9, 12.0, 4.5 Hz), 1.40 (ddd, 1H, $J$ = 13.5, 12.0, 4.5 Hz), 1.25-1.10 (m, 1H), 1.19 (s, 3H), 0.96 (s, 3H), 0.88 (s, 3H); $^{13}C$ NMR (75 MHz, CDCl3) δ 211.5, 145.7, 129.1, 127.4, 127.0, 80.9, 65.2, 55.7, 50.2, 48.7, 45.4, 44.3, 32.4, 29.0, 22.9, 22.8, 10.0. HRMS (EI) calcd for $C_{19}H_{23}OCl$ m/e 302.1437, found m/e 302.1435.

**Tricyclic ketones 31c and 32c.** $TiCl_4$ (70 μL of a 3.70 M solution in $CH_2Cl_2$, 0.26 mmol) was added to a -78 °C solution of dienone **14c** (62 mg, 0.26 mmol) dissolved in 25 mL of $CH_2Cl_2$. After stirring for 1 hour the reaction was warmed to 0 °C and stirred for two hours. Water (20 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 20 mL portions of $Et_2O$ and the organic layers were combined. These combined layers were dried with $MgSO_4$, filtered and concentrated to give a pale yellow oil. Flash column chromatography (silica gel, 1 x 11 cm column, hexanes/EtOAc 19:1) yielded **31c** (37 mg, 0.15mmol, 59%)and **32c** (5 mg, 0.020 mmol, 7%).

**31c:** clear colorless oil; $R_f$ 0.36 (hexanes/EtOAc 9:1); IR (neat) 2959, 1740, 1454 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 2.51 (dd, 1H, *J* = 18, 8.5 Hz), 2.45 (dd, 1H, *J* = 18, 10.5 Hz), 2.15 (ddd, 1H, *J* = 13.5, 9.0, 4.0 Hz), 2.11-2.09 (m, 1H), 1.85 (d, 1H, *J* = 6.5 Hz), 1.83-1.80 (m, 1H), 1.79 (d, 1H, *J* = 4.0 Hz), 1.35 (ddd, 1H, *J* = 13.5, 11.5, 4 Hz), 1.23 (ddd, 1H, *J* = 12, 9.0, 4.0 Hz), 1.19 (d, 3H, *J* = 6.5 Hz), 1.11 (s, 3H), 0.90 (s, 3H), 0.73 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 212.4, 81.2, 64.6, 55.5, 49.8, 48.6, 44.5, 32.5, 32.4, 29.1, 23.5, 22.8, 22.7, 9.9. Anal. calcd for $C_{14}H_{21}OCl$: C, 69.80; H, 8.81. Found: C, 69.66; H, 8.72.

**32c:** clear colorless oil; $R_f$ 0.35 (hexanes/EtOAc 9:1); IR (neat) 2962, 1743 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 2.90 (d, 1H, *J* = 5.0 Hz), 2.65 (dd, 1H, *J* = 20.0, 9.5 Hz), 2.33 (dd, 1H, *J* = 20.0, 2.5 Hz), 2.21-2.15 (m, 1H), 1.95 (dd, 1H, *J* = 4.0, 4.0 Hz), 1.72-1.63 (m, 2H), 1.37-1.19 (m, 2H), 1.22 (d, 3H, *J* = 7.5 Hz), 1.22 (s, 3H), 1.08 (s, 3H), 0.91 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 215.0, 80.6, 62.1, 54.0, 52.5, 51.3, 47.6, 32.7, 28.2, 24.8, 21.3, 20.7, 20.4, 13.0.

**Tricyclic ketones 31d and 32d.** $TiCl_4$ (68 μL of a 3.70 M solution in $CH_2Cl_2$, 0.25 mmol) was added to a -78 °C solution of dienone **14d** (62 mg, 0.25 mmol) dissolved in 25 mL of $CH_2Cl_2$. After 45 minutes the reaction was warmed to 0 °C and stirred for two hours. Water (20 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 20 mL portions of $Et_2O$ and the organic layers were combined. These combined layers were dried with $MgSO_4$, filtered and concentrated. Medium pressure liquid chromatography (silica gel, 1 x 15 cm column, Hexanes/EtOAc 99:1) yielded **31d** (36mg, 0.13 mmol, 50%) and **32d** (12 mg, 0.042 mmol, 16%).

**31d**: white solid, mp 77-79 °C, $R_f$ 0.39 (Hexanes/EtOAc 9:1); IR (KBr) 2959, 1736 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 2.60 (dd, 1H, *J* = 18.0, 5.0 Hz), 2.34 (dd, 1H, *J* = 18.0, 7.0 Hz), 2.16 (ddd, 1H, *J* = 13.5, 9.0, 4.0 Hz), 1.96-1.89 (m, 2H), 1.84-1.77 (m, 1H), 1.69 (d, 1H, *J* = 4.5 Hz), 1.37 (ddd, 1H, *J* = 13.5, 11.5, 4.5 Hz), 1.28 (ddd, 1H, *J* = 13.5, 8.5, 4.5 Hz), 1.12 (s, 3H), 0.90 (s, 12H), 0.76 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 212.6, 81.4, 57.8, 55.4, 51.9, 49.0, 48.4, 38.4, 33.3, 32.5, 29.1, 27.2, 22.8, 22.7, 10.0.

**32d**: clear colorless oil, $R_f$ 0.38 (hexanes/EtOAc 9:1); IR (neat) 2961, 1742 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 3.06 (dd, 1H, *J* = 5.0, 5.0 Hz), 2.68 (dd, 1H, *J* = 20.0, 8.0 Hz), 2.41 (dd, 1H, *J* = 20.0, 10.0 Hz), 1.89 (ddd, 1H, *J* = 10.0, 7.5, 4.5 Hz), 1.81 (dd, 1H, *J* = 4.5, 4.5 Hz), 1.70-1.60 (m, 2H), 1.47-1.36 (m, 2H), 1.24 (s, 3H), 1.10 (s, 3H), 0.92 (s, 3H), 0.91 (s, 9H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 213.5, 81.5, 55.3, 53.3, 53.2, 52.4, 44.4, 41.3, 33.3, 32.1, 27.5, 20.8, 20.7, 20,6, 13.6. HRMS (EI) calcd for $C_{17}H_{27}OCl$ m/e 282.1750, found m/e 282.1727.

**Tricyclic ketones 31e and 33.** $TiCl_4$ (70 μL of a 3.70 M solution in $CH_2Cl_2$, 0.26 mmol) was added to a -78 °C solution of dienone **14e** (73 mg, 0.26 mmol) dissolved in 26 mL of $CH_2Cl_2$ turning the solution a very dark red/brown. After 10 minutes the reaction was complete by TLC and water (15 mL) was added to quench the reaction and warmed to room temperature. The phases were separated and the aqueous phase was washed with 2 x 20 mL portions of $Et_2O$. The organic layers were combined and dried with $MgSO_4$, filtered and concentrated. Radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 99:1 ramped to hexanes/EtOAc 9:1) yielded **31e** (22 mg, 0.070 mmol, 25%) and **33** (19 mg, 0.070 mmol, 25%).

**31e:** white solid: mp 73-75 °C; $R_f$ 0.71 (hexanes/EtOAc 9:1); IR (KBr) 3015, 2960, 1739 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38-7.25 (m, 5H), 2.94 (dq, 1H, $J$ = 7.0, 11.5 Hz), 2.69 (dd, 1H, $J$ = 11.5, 7.0, Hz), 2.32 (d, 1H, $J$ = 7.0 Hz), 2.20 (ddd, 1H, $J$ = 13.5, 9.5, 4.5 Hz), 1.84 (d, 1H, $J$ = 4.0 Hz), 1.82-1.76 (m, 1H), 1.39 (ddd, 1H, $J$ = 13.5, 11.5, 4.0 Hz), 1.20 (s, 3H), 1.21-1.15 (m, 1H), 1.07 (d, 3H, $J$ = 7.0 Hz), 0.94 (s, 3H), 0.75 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 212.7, 144.8, 129.1, 127.8, 127.1, 80.3, 63.1, 55.5, 52.8, 49.6, 49.6, 48.4, 32.4, 29.1, 23.0, 22.8, 13.3, 10.0. Anal. calcd for $C_{20}H_{25}OCl$, C, 75.81; H, 7.95. Found, C, 75.60; H, 8.07.

**33:** white solid, mp 151-153 °C; $R_f$ 0.38 (hexanes/EtOAc 9:1); IR (KBr) 2939, 1753 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.33-7.25 (m, 3H), 7.14-7.11 (m, 2H), 3.47 (d, 1H, $J$ = 2.5 Hz), 2.34 (br d, 1H, $J$ = 2.5 Hz), 2.17 (ddd, 1H, $J$ = 14.5, 12.0, 2.5 Hz), 2.08 (br d, 1H, $J$ = 3.0 Hz), 1.79 (ddd, 1H, $J$ = 12.0, 9.5, 3.0 Hz), 1.62-1.55 (m, 1H), 1.53-1.46 (m, 1H), 1.32 (s, 3H), 1.22 (s, 3H), 1.19 (s, 3H), 1.00 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 174.2, 140.9, 129.0, 128.9, 127.6, 103.8, 89.0, 57.1, 56.0, 51.1, 50.6, 44.4, 27.1,

26.8, 25.2, 22.8, 20.1, 18.0. HRMS (EI) calcd for $C_{20}H_{24}O$ m/e 268.18272, found m/e 268.18295.

**Tricyclic ketones 34.** $BF_3 \bullet O_2Et$ (119 μL, 0.960 mmol) was added to a -78 °C solution of dienone **24a** (60 mg, 0.24 mmol) dissolved in 24 mL of $CH_2Cl_2$. After stirring for 30 minutes the reaction was warmed to -20 °C and stirred for seventeen hours. Water (20 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 20 mL of $Et_2O$ and the organic layers were combined. The combined layers were dried with $MgSO_4$, filtered and concentrated to give a pale yellow oil. Radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 19:1) yielded **34a** and **34b** as a 1:2 ratio of diastereomers (30 mg, 0.17 mmol, 70%).

**34b**: white solid, mp 58-60 °C; $R_f$ 0.12 (hexanes/EtOAc 9:1); IR (KBr) 2914, 2864, 1692 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, 1H, *J* = 6.0, 3.0 Hz), 6.20 (dd, 1H, *J* = 6.0, 3.0 Hz), 3.15 (ddddd, 1H, *J* = 11.5, 9.0, 5.5, 3.0, 3.0 Hz), 2.78 (dd, 1H, *J* = 6.0, 3.0 Hz), 2.31 (ddd, 1H, *J* = 6.0, 6.0, 3.5 Hz), 2.20 (dddd, 1H, *J* = 13.5, 11.0, 3.0, 3.0 Hz), 2.03-1.93 (m, 2H), 1.85 (ddd, 1H, *J* = 13.5, 3.0, 3.0 Hz), 1.25 (s, 3H), 0.95 (d, 1H, *J* = 11.0 Hz), 0.94 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 213.8, 172.6, 134.1, 49.6, 43.2, 42.4, 38.9, 36.5, 29.7, 26.1, 25.3, 20.8. HRMS (EI) calcd for $C_{12}H_{16}O$ m/e 176.1201, found m/e 176.1203.

**Tricyclic ketone 37 and 38.** $TiCl_4$ (57 mL of a 3.70 M solution in $CH_2Cl_2$, 0.21 mmol) was added to a -78 °C solution of dienone **24b** (53 mg, 0.21 mmol) dissolved in 21 mL of $CH_2Cl_2$. After stirring for 30 minutes the reaction was warmed to -20 °C and stirred for two weeks. Water (20 mL) was added to quench the reaction, warmed to room temperature and the phases were separated. The aqueous phase was washed with 2 x 25

mL portions of $Et_2O$ and the organic layers were combined. These combined organic layers were dried with $MgSO_4$, filtered and concentrated to give a yellow oil. Radial chromatography (silica gel, 2mm plate, hexanes/EtOAc 99:1 ramped to hexanes/EtOAc 9:1) yielded **37** (30 mg, 0.10 mmol, 48%) and **38** (7 mg, 0.024 mmol, 12%).

**37:** very pale yellow oil, $R_f$ 0.35 (hexanes/EtOAc 9:1); IR (neat) 1738; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.38-7.34 (m, 2H), 7.30-7.25 (m, 3H), 4.25 (s, 1H), 3.07 (ddd, 1H, *J* = 12.0, 10.5, 7.0 Hz), 2.92-2.85 (m, 2H), 2.49 (dd, 1H, *J* = 18.5, 12.0 Hz), 2.14 (br s, 1H), 2.11 (ddd, 1H, *J* = 13.0, 8.5, 2.5 Hz), 1.88-1.82 (m, 2H), 1.56 (ddd, 1H, *J* = 13.0, 5.5, 3.5 Hz), 1.13 (s, 3H), 0.98 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 214.3, 142.0, 129.0, 127.3, 127.1, 69.6, 69.2, 52.2, 49.6, 47.6, 44.1, 39.9, 38.4, 34.0, 30.1, 23.2. HRMS (EI) calcd for $C_{18}H_{21}OCl$ m/e 288.12809, found m/e 288.12939.

**38:** pale yellow oil, $R_f$ 0.38 (hexanes/EtOAc 9:1); IR (neat) 2957, 1717 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) δ 7.33-7.29 (m, 2H), 7.24-7.21 (m, 1H), 7.25-7.10 (m, 2H), 3.31 (ddd, 1H, *J* = 6.5, 3.5, 3.5 Hz), 3.08 (dd, 1H, *J* = 16.0, 7.5 Hz), 2.85 (ddd, 1H, *J* = 16.0, 4.0, 2.5 Hz), 2.80-2.74 (m, 1H), 2.69 (ddd, 1H, *J* = 14.0, 3.5, 3.5 Hz), 2.34-2.27 (m, 1H), 2.22 (d, 1H, *J* = 3.5 Hz), 2.13 (d, 1H, *J* = 14.0 Hz), 1.97 (dd, 1H, *J* = 3.5, 3.5 Hz), 1.39 (s, 3H), 1.25-1.27 (m, 1H), 1.10 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 206.3, 145.1, 129.1, 127.2, 126.8, 58.8, 50.8, 48.0, 46.4, 43.3, 42.1, 38.3, 33.8, 24.0, 22.7. HRMS (EI) calcd for $C_{18}H_{21}OCl$ m/e 288.12809, found 288.12890.

**Tricyclic ketones 42 and 43.** $TiCl_4$ (69 μL of a 3.70 M solution in $CH_2Cl_2$, 0.26 mmol) was added to a -78 °C solution of dienone **24e** (68 mg, 0.26 mmol) dissolved in 25 mL of $CH_2Cl_2$ turning the solution a dark reddish/brown. After 10 minutes the reaction was quenched with water (20 mL) at -78 °C and allowed to warm to room temperature.

The phases were separated and the aqueous washed with 2 x 25 mL portions of $Et_2O$. The organic layers were combined and dried with $MgSO_4$, filtered and concentrated to give a yellow oil. Radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 99:1 ramped to Hexanes/EtOAc 19:1) yielded **42** (25 mg, 0.086 mmol, 33%) and **43** (20 mg, 0.075 mmol, 29%).

**42:** clear colorless oil, $R_f$ 0.50 (hexanes/EtOAc 9:1); IR (neat) 2965, 2931, 2871, 1737 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38-7.35 (m, 2H), 7.29-7.27 (m, 3H), 4.27 (s, 1H), 2.84-2.79 (m, 1H), 2.52 (dd, 1H, *J* = 12.0, 10.5 Hz), 2.41 (dq, 1H, *J* = 11.5, 6.5 Hz), 2.10 (d, 1H, *J* = 3.0 Hz), 1.98 (ddd, 1H, *J* = 11.0, 8.0, 3.0 Hz), 1.83 (d, 1H, *J* = 10.5 Hz), 1.74 (dd, 1H, *J* = 10.5, 1.5 Hz), 1.45 (ddd, 1H, *J* = 13.0, 5.5, 3.5 Hz), 1.13 (s, 3H), 1.03 (d, 3H, *J* = 7.0 Hz), 0.96 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 215.8, 141.1, 129.0, 127.7, 127.3, 70.1, 68.3, 56.3, 55.9, 51.9, 42.3, 40.0, 38.4, 33.1, 30.1, 23.1, 12.8. HRMS (EI) calcd for $C_{19}H_{23}OCl$ m/e 302.1437, found m/e 302.1413.

**43:** colorless oil: $R_f$ 0.40 (hexanes/EtOAc 9:1); IR (neat) 2923, 1691, 1626; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.50-7.39 (m, 5H), 3.54 (dddd, 1H, *J* = 11.5, 6.5, 3.0, 3.0 Hz), 2.97 (dd, 1H, *J* = 3.0, 6.5 Hz), 2.41 (ddd, 1H, *J* = 3.0, 5.5, 5.5 Hz), 2.07 (dddd, 1H, *J* = 16.0, 11.0, 2.5, 2.5 Hz), 2.02-1.96 (m, 1H), 1.86-1.82 (m, 1H), 1.64 (ddd, 1H, *J* = 9.0, 3.0, 3.0 Hz), 1.90 (d, 3H, *J* = 3.0 Hz), 1.25 (s, 3H), 1.00 (s, 3H), 0.93 (d, 1H, *J* = 10.5 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 212.4, 175.0, 137.2, 135.9, 129.3, 128.8, 128.6, 49.5, 43.7, 42.2, 39.3, 36.0, 29.7, 26.1, 25.6, 21.0, 10.0. HRMS (EI) calcd for $C_{19}H_{22}O$ m/e 266.16707, found m/e 266.16720.

**Tricyclic ketones 44.** $TiBr_4$ (210 μL of a 1.0 M solution in $CH_2Cl_2$, 0.21 mmol) was added to a -78 °C solution of dienone **14b** (51 mg, 0.19 mmol) dissolved in 20 mL of

$CH_2Cl_2$. After stirring for 30 minutes the reaction was warmed to 0 °C and allowed to warm slowly to room temperature overnight. Water (20 mL) was used to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 25 ml portions of $Et_2O$ and the organic layers were combined. These combined organic layers were dried with $MgSO_4$, filtered and concentrated to give a very pale yellow oil. Radial chromatography (silica gel, 2mm plate, hexanes/EtOAc 99:1) yielded **44a** (14 mg, 0.041 mmol, 21%) and **44b** (41 mg, 0.12 mmol, 62%).

**44a**: white solid, mp 118-119 °C; $R_f$ 0.60 (hexanes/EtOAc 9:1); IR (KBr) 2963, 1729 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.38-7.24 (m, 5H), 3.27 (ddd, 1H, $J$ = 11.0, 8.5, 6.5 Hz), 3.13 (dd, 1H, $J$ = 18.5, 11.0 Hz), 2.81 (dd, 1H, $J$ = 18.5, 8.5 Hz), 2.55 (d, 1H, $J$ = 6.5 Hz), 2.21 (ddd, 1H, $J$ = 13.5, 9.5, 4.5 Hz), 1.87 (d, 1H, $J$ = 4.5 Hz), 1.82-1.75 (m, 1H), 1.52 (ddd, 1H, $J$ = 13.5, 12.0, 4.5 Hz), 1.20 (s, 3H), 1.20-1.15 (m, 1H), 0.99 (s, 3H), 0.87 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 211.4, 145.7, 129.2, 127.4, 127.0, 78.8, 65.6, 55.8, 50.3, 47.6, 44.9, 44.7, 35.1, 29.0, 23.1, 22.9, 10.5. HRMS (EI) calcd for $C_{19}H_{23}OBr$ m/e 346.0932, found m/e 346.0923.

**44b**: clear colorless oil, $R_f$ 0.57 (hexanes/EtOAc 9:1); IR (neat) 2962, 1735 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.40-7.33 (m, 4H), 7.26-7.23 (m, 1H), 3.45 (dd, 1H, $J$ = 4.5, 4.5 Hz), 3.31 (ddd, 1H, $J$ = 10.5, 7.0, 3.5 Hz), 3.07 (dd, 1H, $J$ = 20.0, 7.0 Hz), 2.91 (ddd, 1H, $J$ = 20.0, 10.0, 1.0 Hz), 1.99 (dd, 1H, $J$ = 4.5, 4.5 Hz), 1.81-1.71 (m, 2H), 1.59-1.53 (m, 2H), 1.25 (s, 3H), 1.21 (s, 3H), 0.96 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 212.6, 146.6, 129.1, 127.5, 126.8, 77.2, 63.0, 53.5, 53.1, 51.7, 46.7, 40.2, 31.8, 20.9, 20.8, 20.6, 15.7. HRMS (EI) calcd for $C_{19}H_{23}OBr$ m/e 346.0932, found m/e 346.0931.

**Tricyclic ketone 45**. $TiI_4$ (63 mg, 0.11 mmol) was added to a -78 °C solution of dienone **14b** (30 mg, 0.11 mmol) dissolved in 12 mL of $CH_2Cl_2$. After stirring for one hour the Lewis Acid was dissolved and the reaction was warmed to room temperature and stirred for thirteen hours. Water (10 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 10 mL portions of $Et_2O$ and the organic layers were combined. These combined layers were dried with $MgSO_4$, filtered and concentrated to give a bright purple oil. Flash column chromatography (silica gel, 1 x 10 cm, hexanes/EtOAc 99:1) yielded **45** (15 mg, 0.056 mmol, 51%): white solid, mp 103-105 °C; $R_f$ 0.52 (hexanes/EtOAc 9:1); IR (KBr) 2950, 2925, 1728 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.36-7.33 (m, 2H), 7.28-7.22 (m, 3H), 3.38 (ddd, 1H, *J* = 15.5, 11.5, 11.5 Hz), 2.76 (dd, 1H, *J* = 19.0, 8.5 Hz), 2.54 (ddd, 1H, *J* = 19.0, 11.5, 2.0 Hz), 2.39 (dd, 1H, *J* = 11.0, 7.0 Hz), 2.30 (br d, 1H, *J* = 11.0 Hz), 1.93 (d, 1H, *J* = 4.5 Hz), 1.80-1.74 (m, 1H), 1.49 (ddd, 1H, *J* = 12.5, 12.5, 4.5 Hz), 1.17 (s, 3H), 1.22-1.16 (m, 1H), 1.08 (ddd, 1H, J = 13.5, 9.5, 4.5 Hz), 0.87 (s, 3H), 0.86 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 219.7, 146.7, 129.0, 127.2, 126.6, 60.7, 55.2, 52.7, 50.2, 48.1, 47.8, 44.5, 37.8, 29.2, 23.2, 21.1, 12.4. HRMS (EI) calcd for $C_{19}H_{24}O$ m/e 268.18272, found 268.18380.

**Tricyclic ketone 46**. $TiF_4$ (230 μL of a 0.50 M solution in $CH_3CN$, 0.11 mmol) was added to a -78 °C solution of dienone **14b** (30 mg, 0.11 mmol) dissolved in 11 mL of $CH_2Cl_2$. After stirring for one hour the reaction was warmed to room temperature and stirred for seven hours. Water (10 mL) was added to quench the reaction and the phases were separated. The aqueous phase was washed with 2 x 15 mL portions of $Et_2O$ and the organic layers were combined. These combined layers were dried with $MgSO_4$, filtered

and concentrated to give a very pale yellow oil. Radial chromatography (silica gel, 2 mm plate, hexanes/EtOAc 99:1 ramped to hexanes/EtOAc 19:1) yielded **46** as a white solid (17 mg, 0.060 mmol, 53%): mp 110-112 °C, $R_f$ 0.44 (hexanes/EtOAc 9:1); IR (KBr) 3483, 2958, 2934, 1728 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 2H), 7.24-7.17 (m, 3H), 2.23 (br d, 1H, $J$ = 10.5 Hz), 3.00-2.93 (m, 2H), 2.67 (s, 1H), 2.51 (br d, 1H, $J$ = 20.0 Hz), 2.02 (dd, 1H, $J$ = 5.0, 5.0 Hz), 1.84-1.77 (m, 1H), 1.51-1.64 (m, 2H), 1.09 (s, 3H), 1.09-1.03 (m, 1H), 0.95 (s, 3H), 0.89 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 219.7, 148.5, 129.0, 127.3, 126.4, 87.8, 58.1, 53.2, 51.4, 50.7, 48.9, 39.8, 31.7, 21.6, 20.3, 20.1, 10.6. HRMS (EI) calcd for $C_{19}H_{24}O_2$ m/e 284.17763, found 284.17691.

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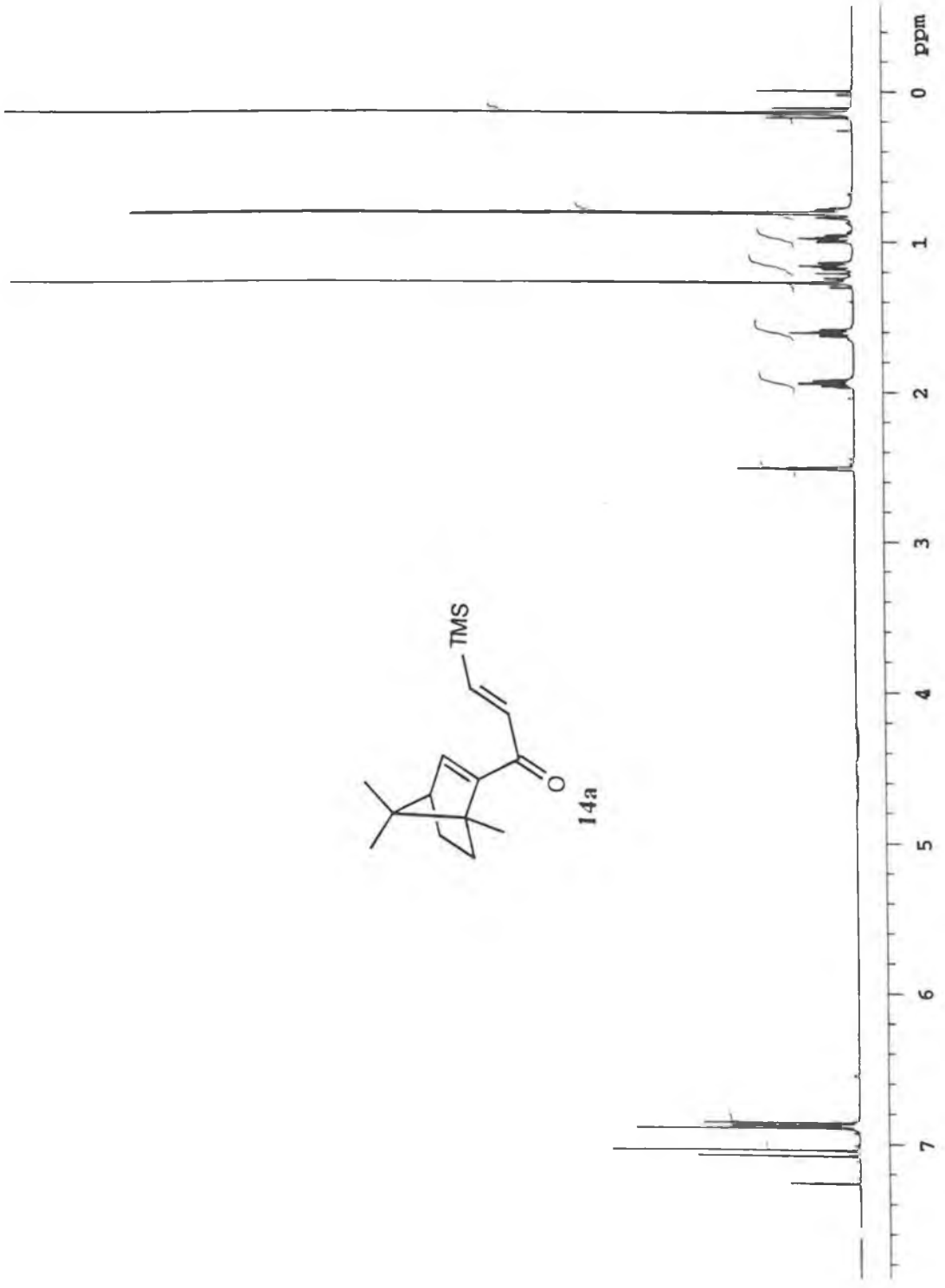
# APPENDIX

## SELECTED NMR SPECTRA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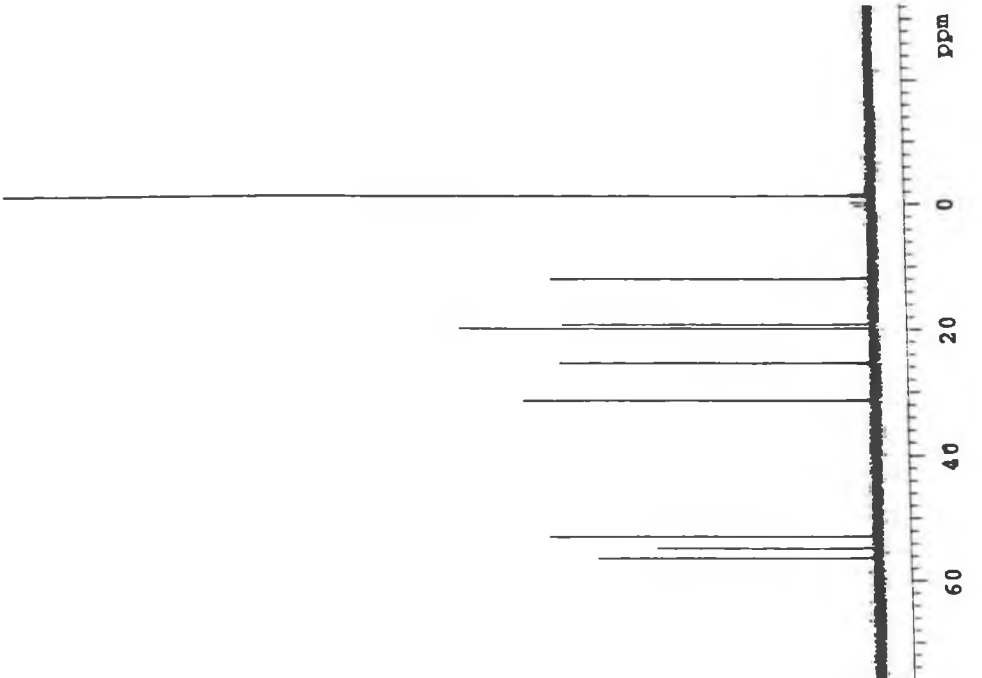
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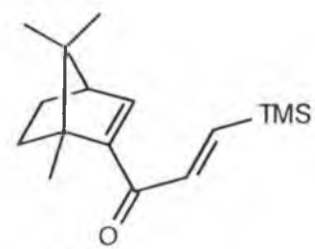


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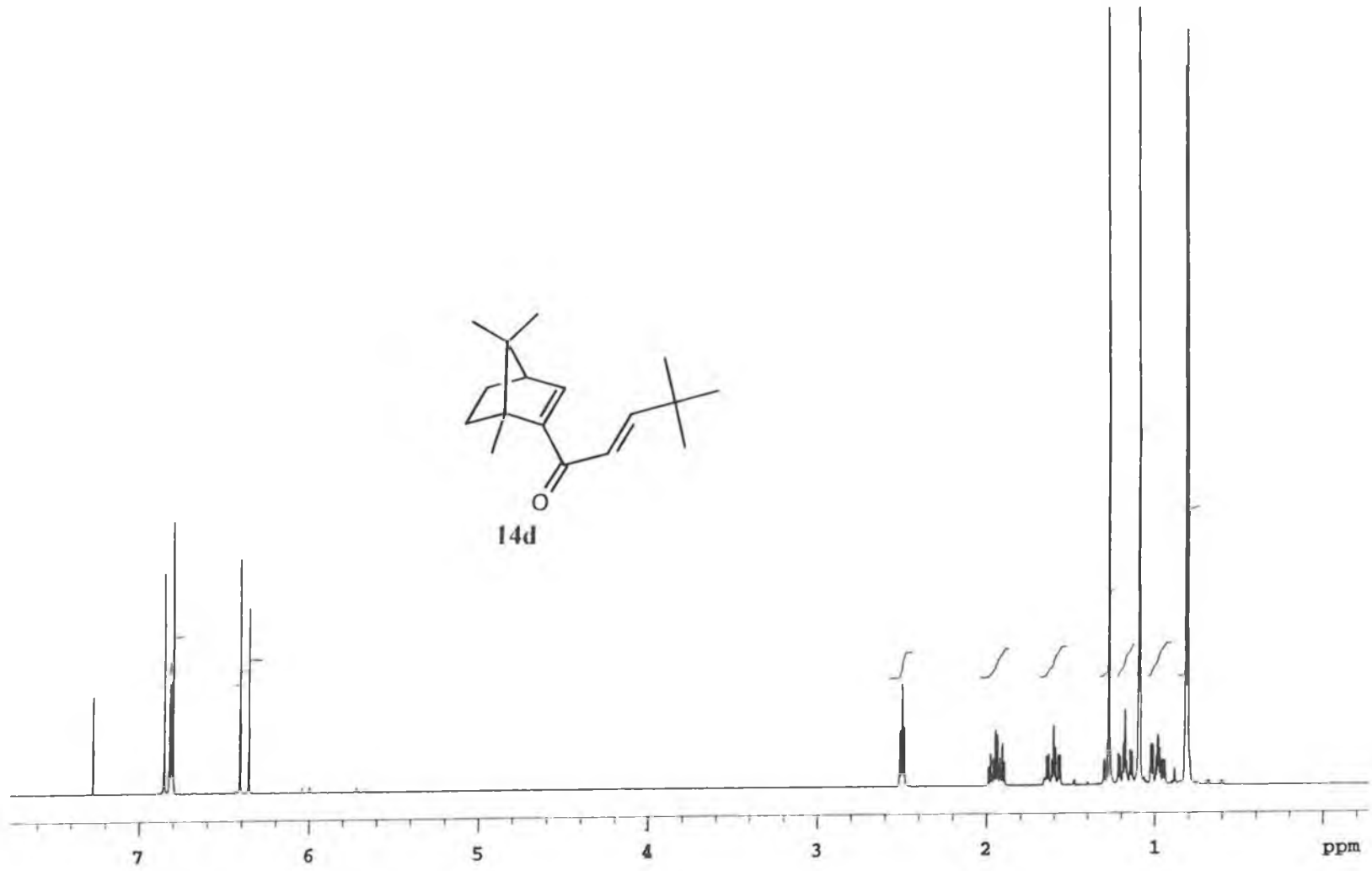


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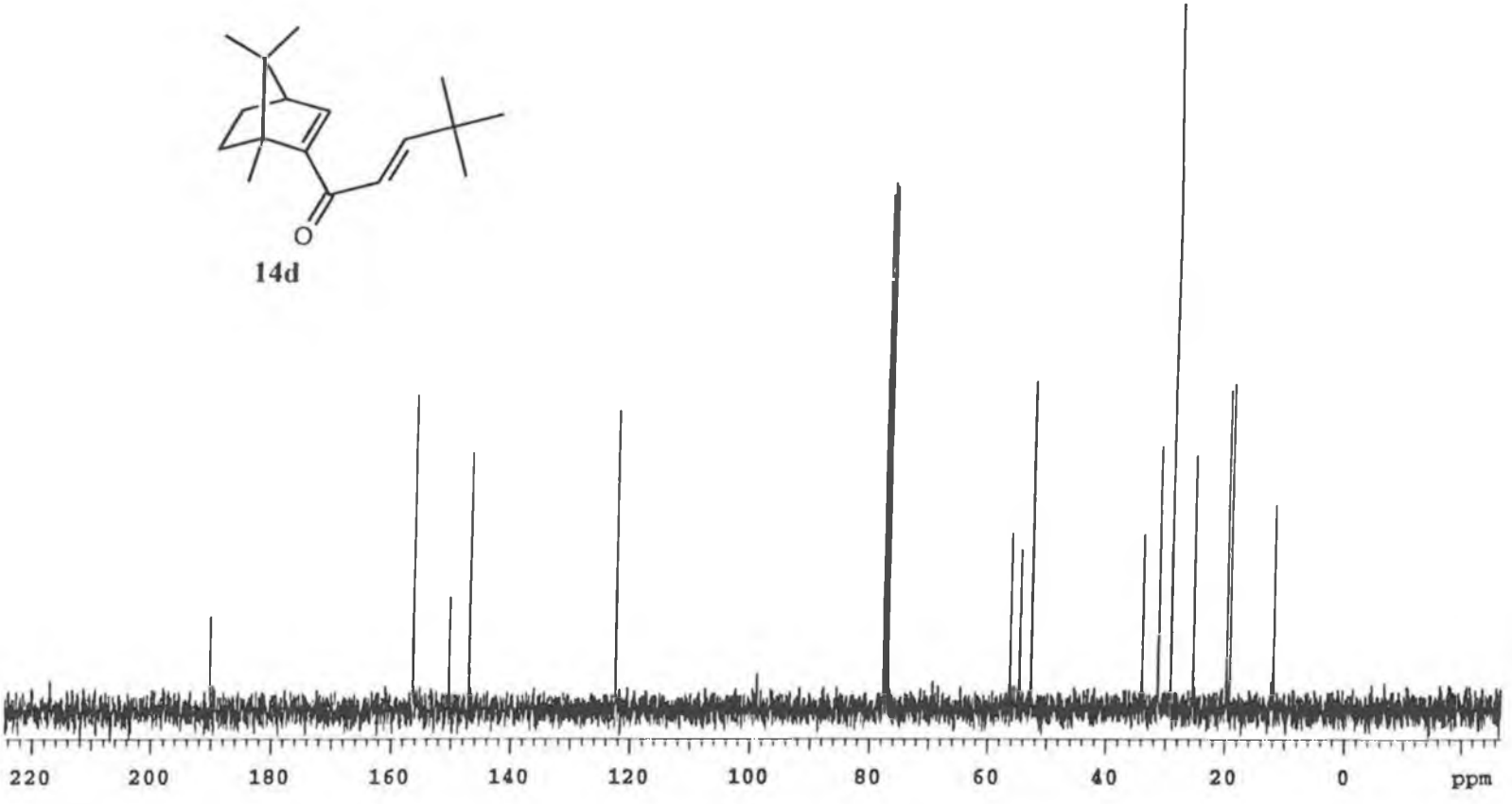


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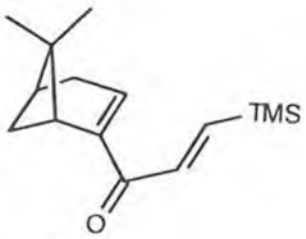


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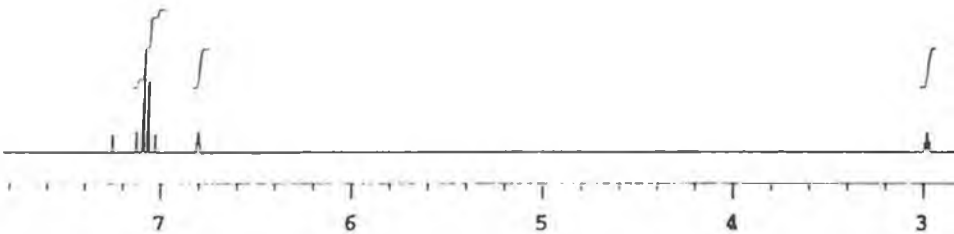

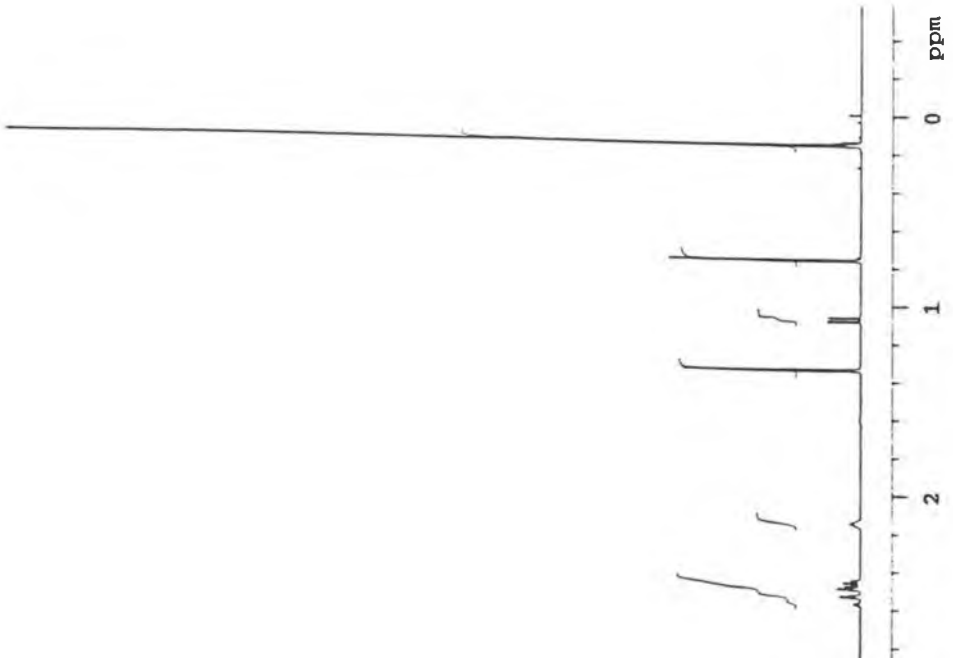
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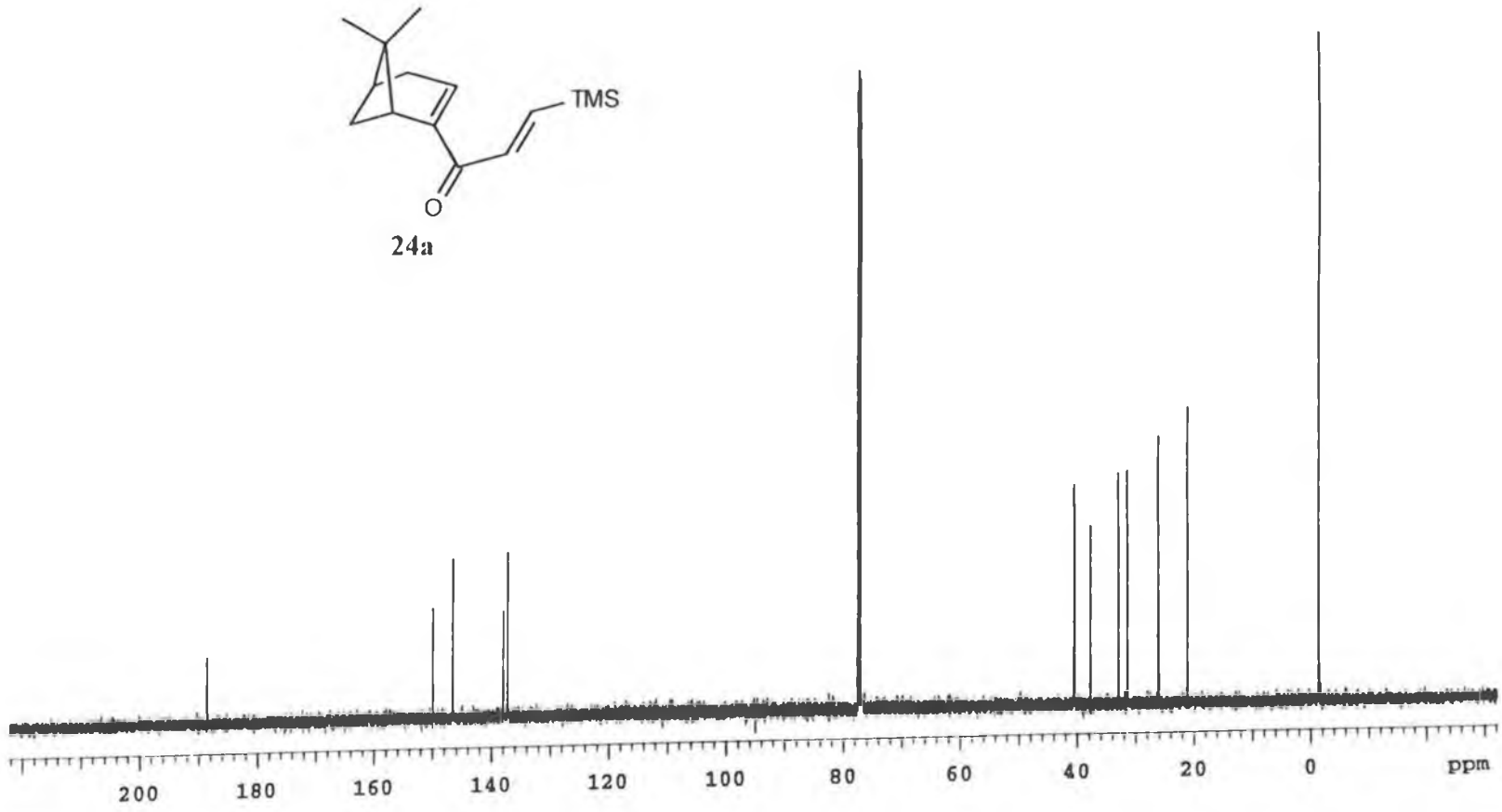


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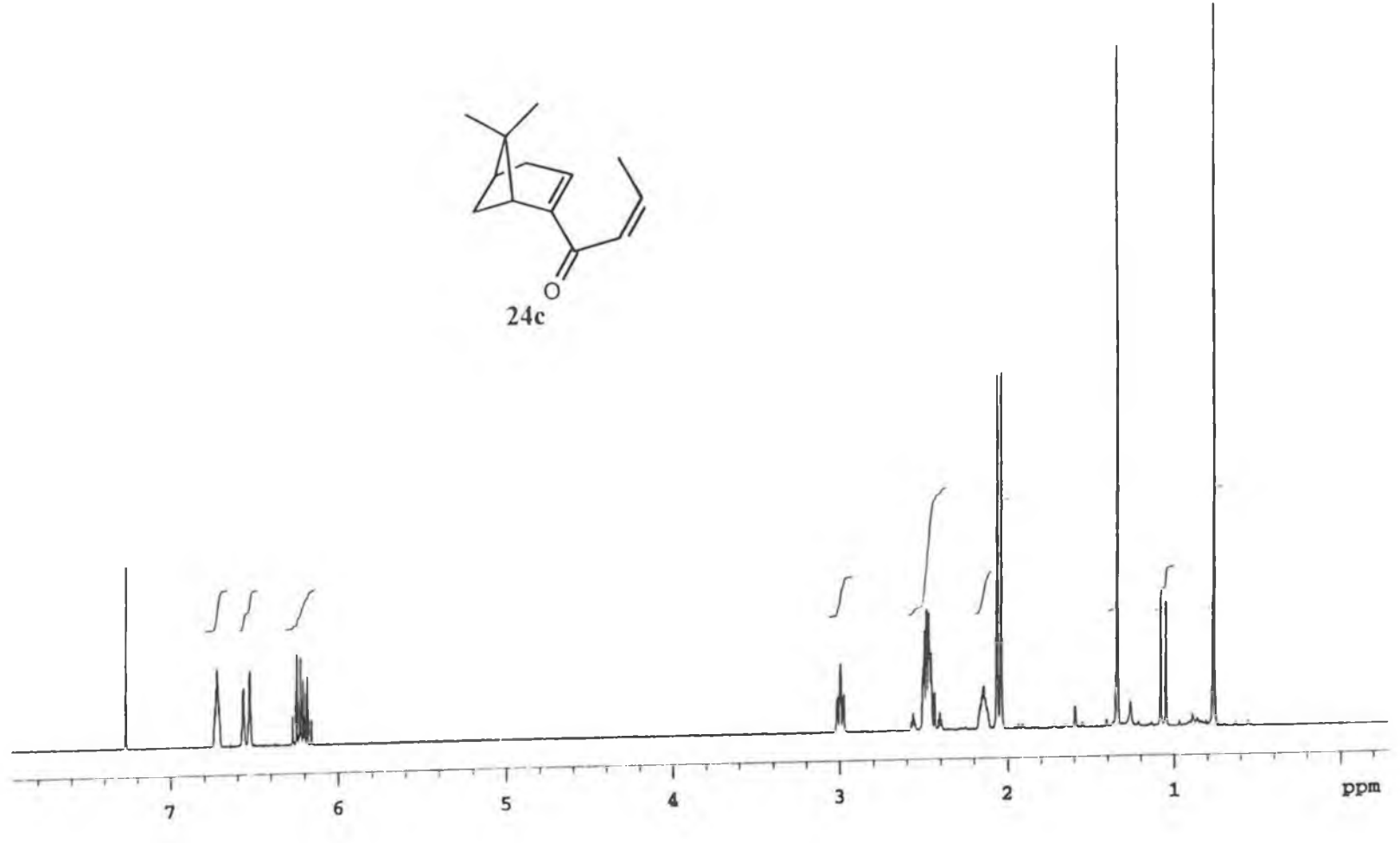


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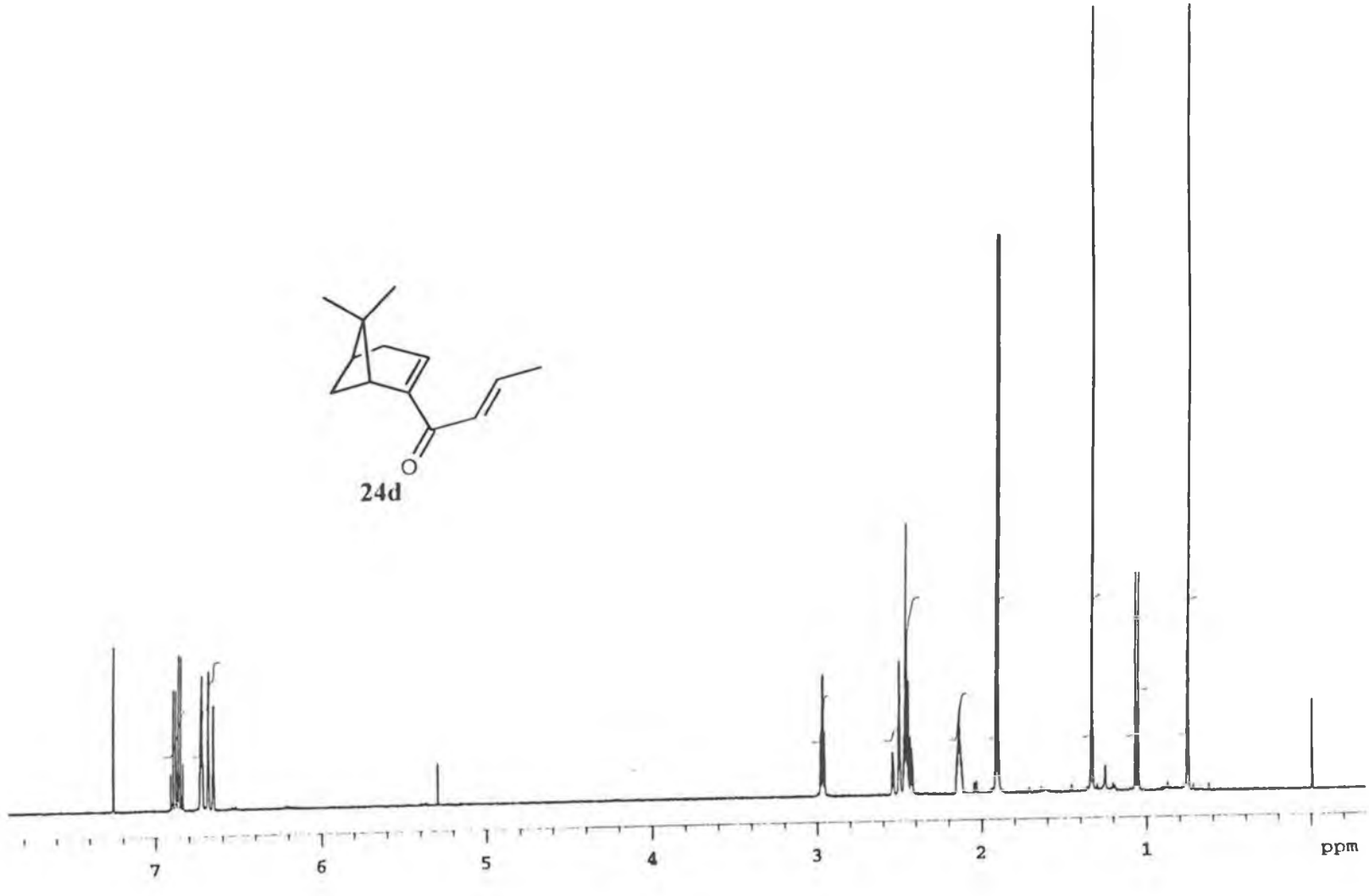
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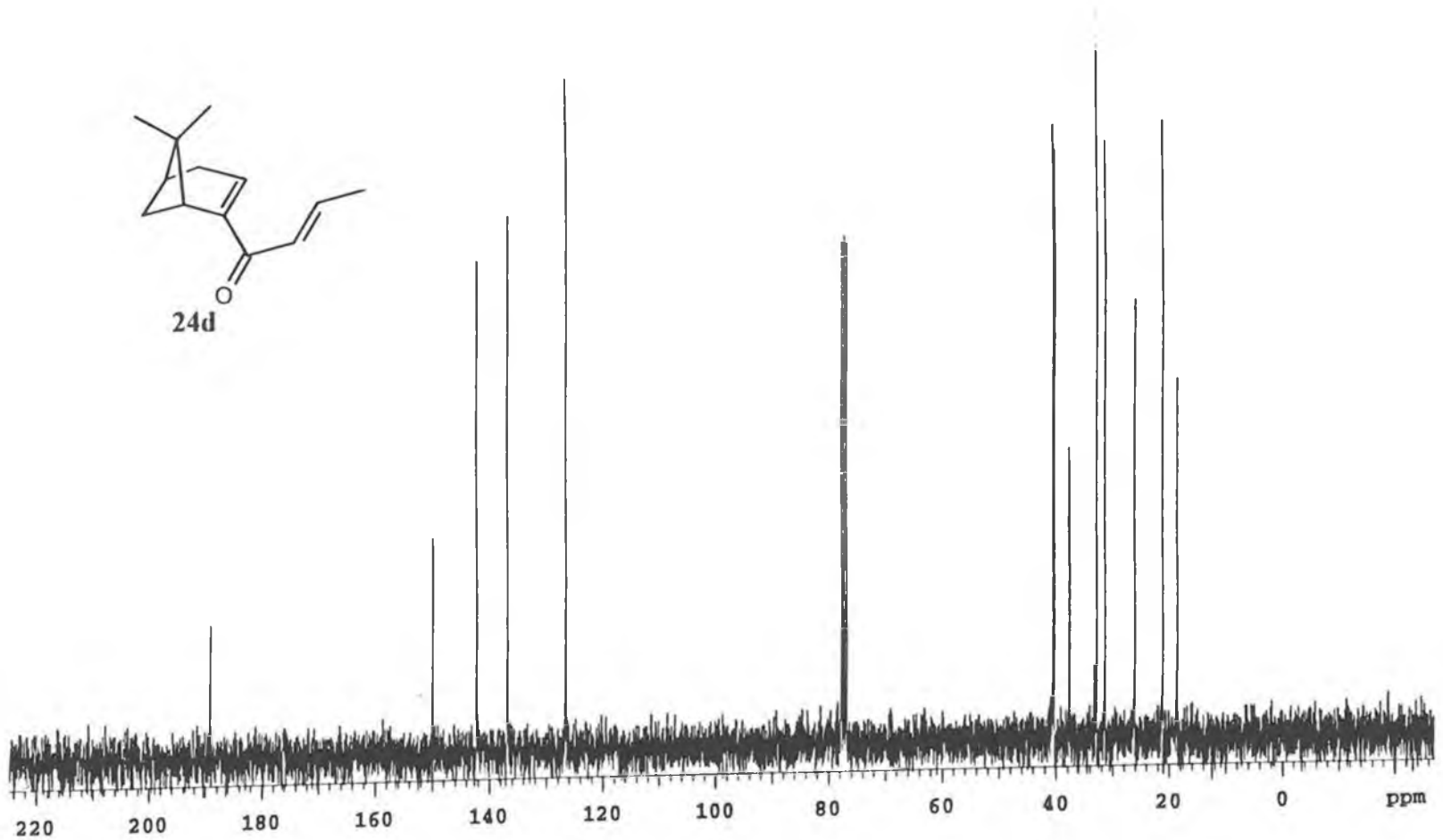
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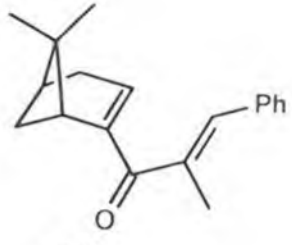


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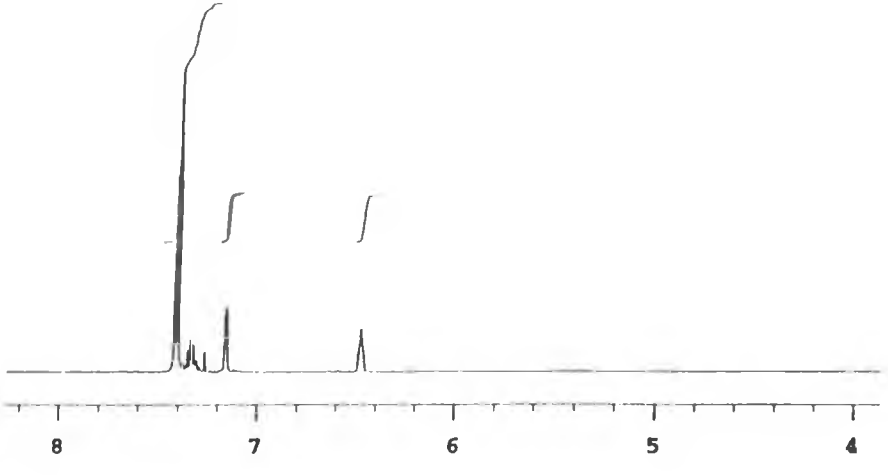

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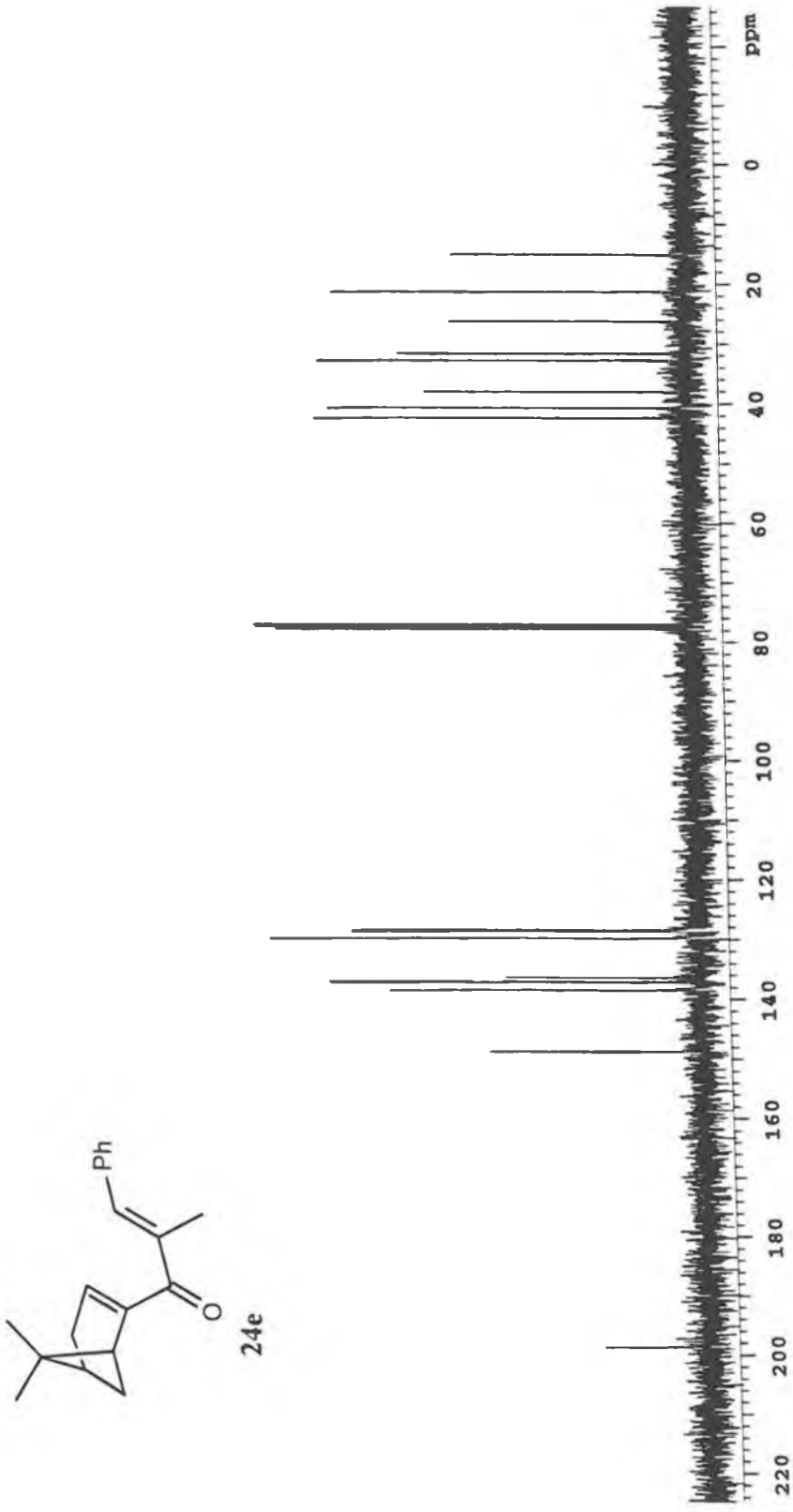


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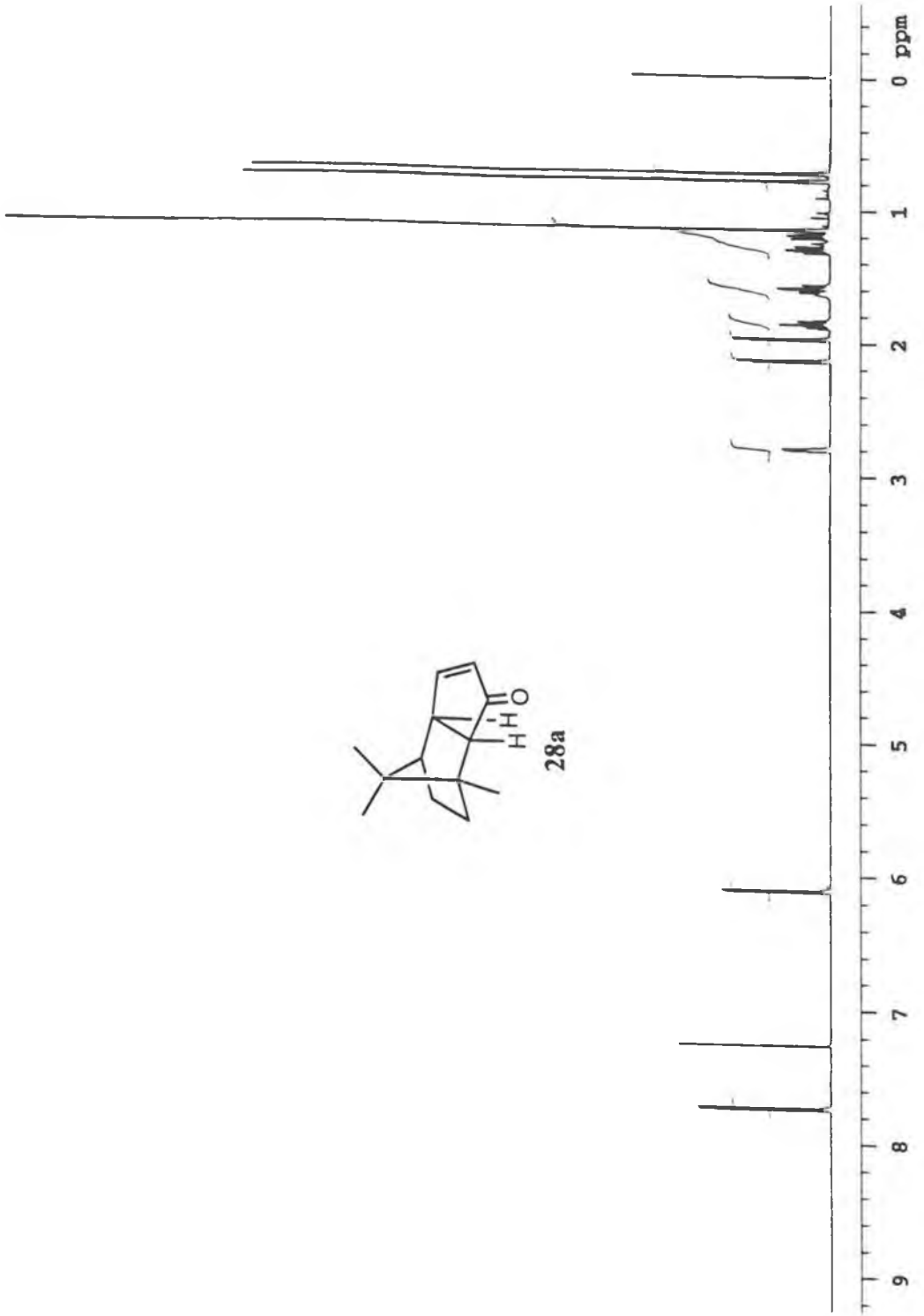
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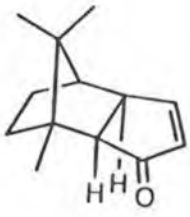


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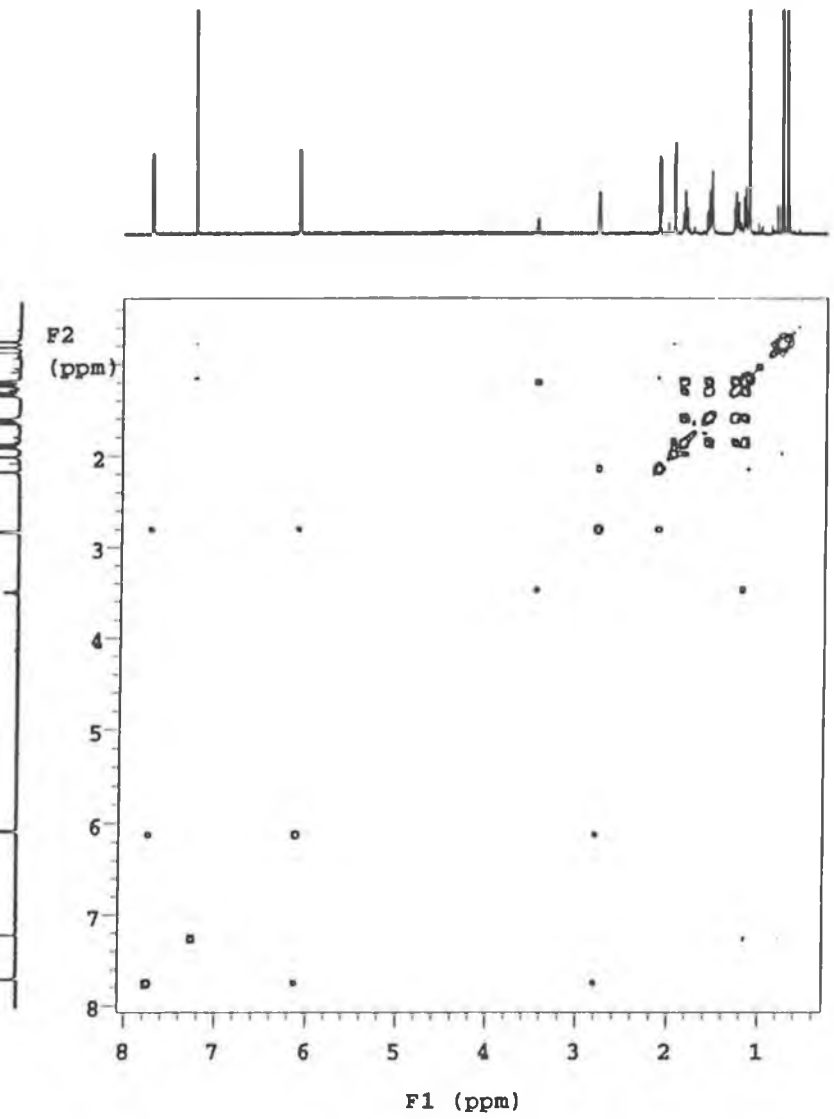
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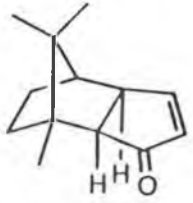


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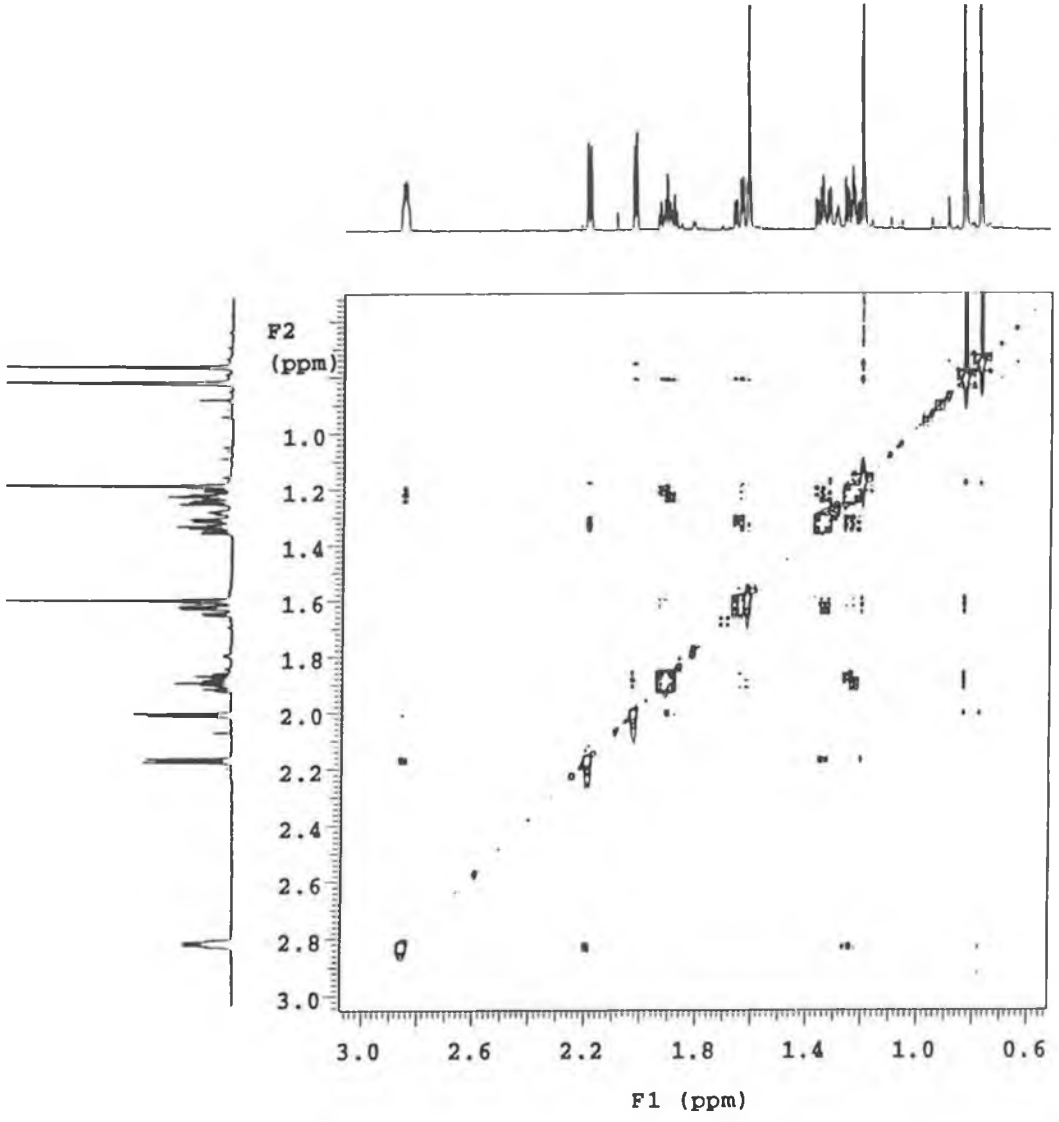
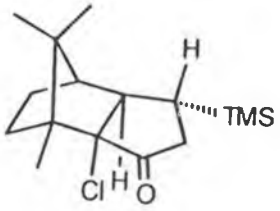
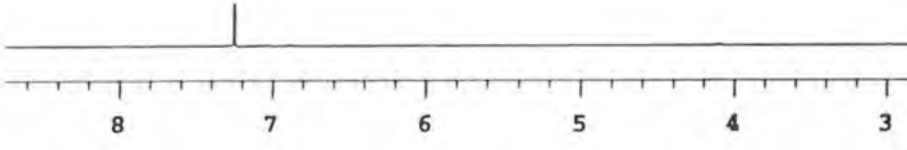
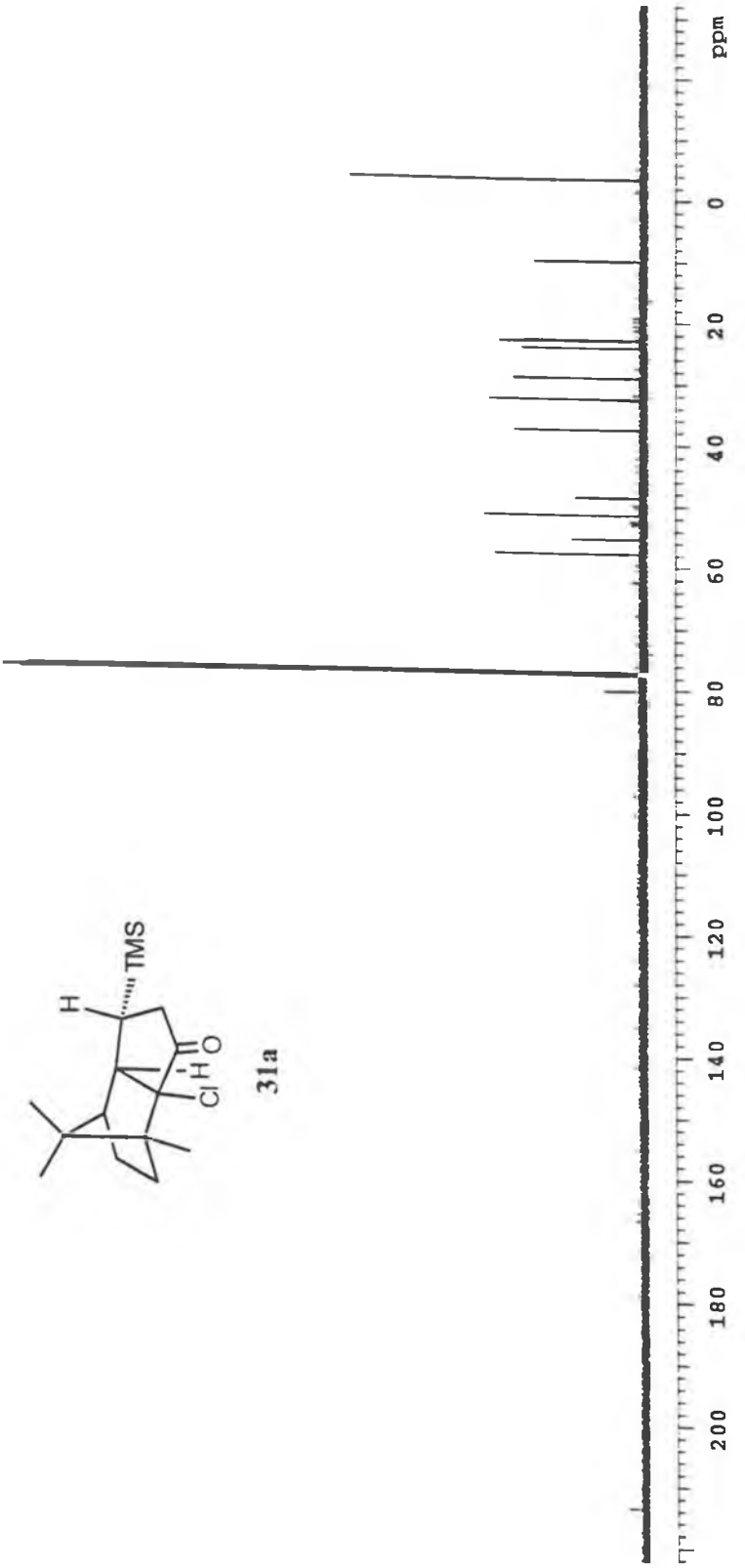




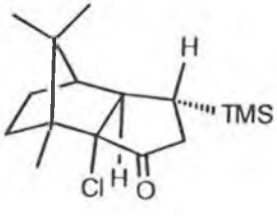

**31a**



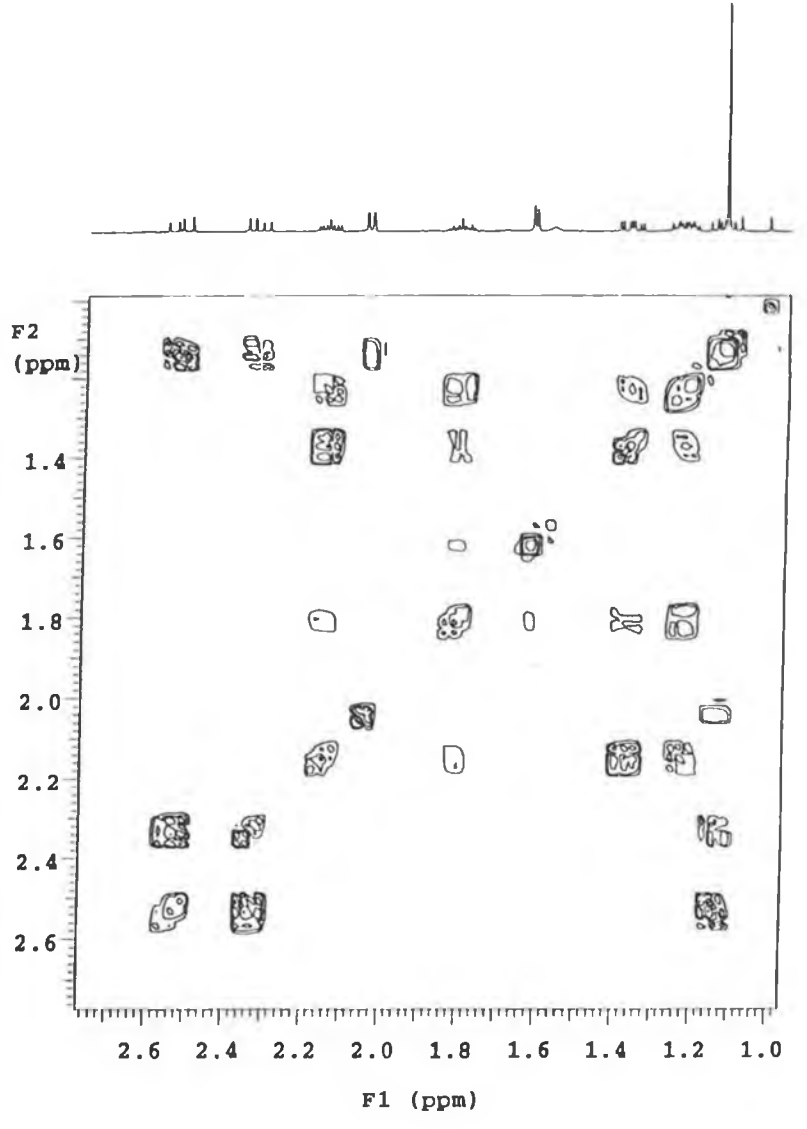
2
1
-0
ppm


TMS
H
Cl
H
O
31a
200
180
160
140
120
100
80
60
40
20
0
ppm

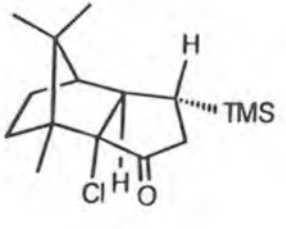
**COSY of**



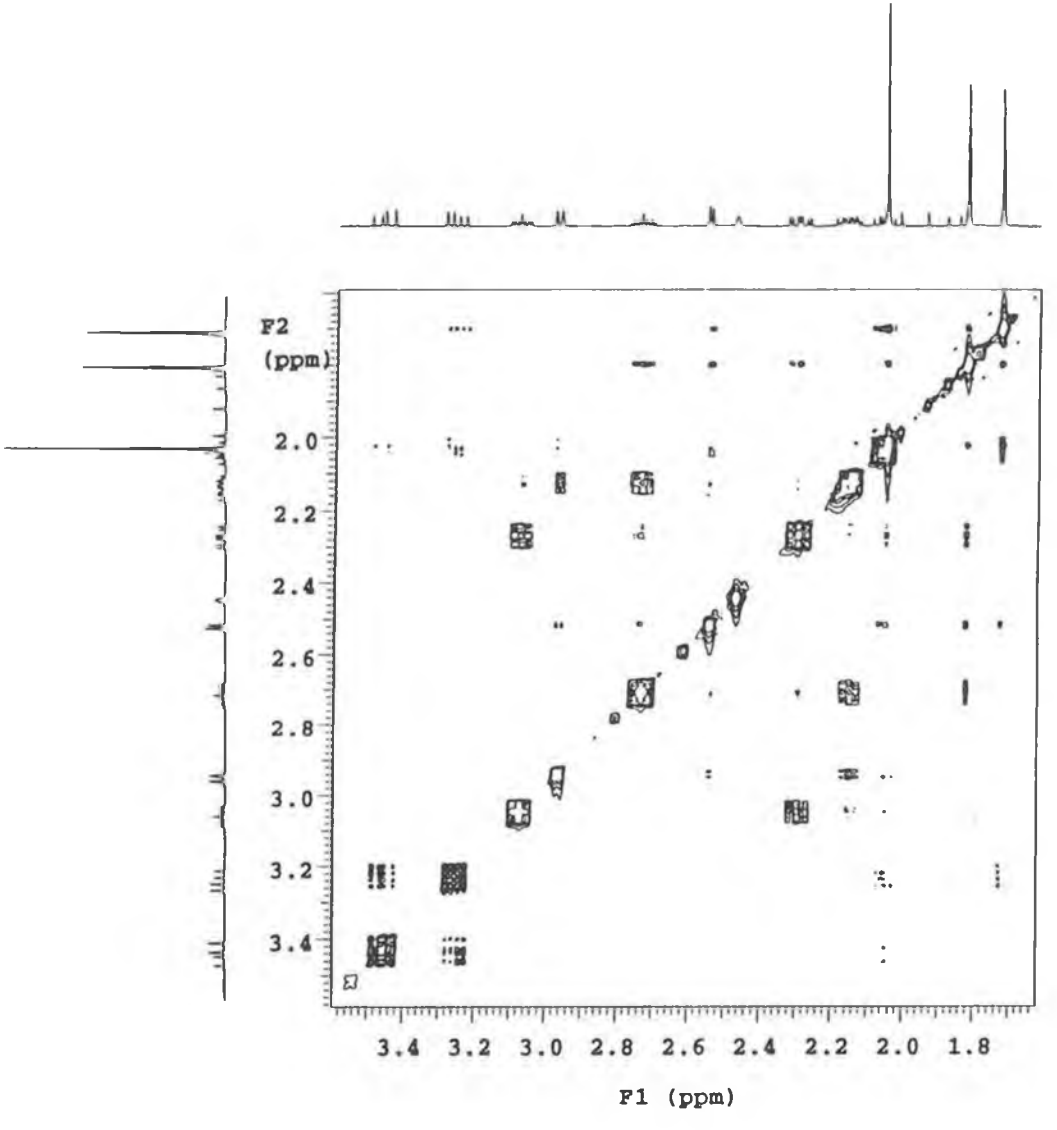

**31a**

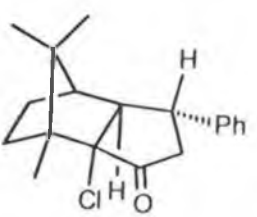

F2
(ppm)
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0
F1 (ppm)

**NOESY of**

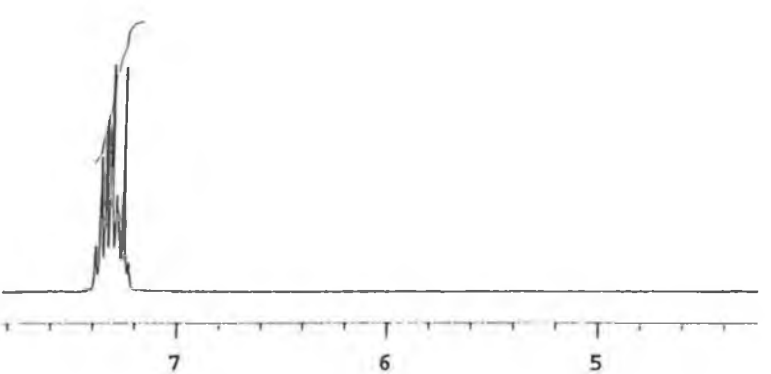

H
TMS
Cl
H
O

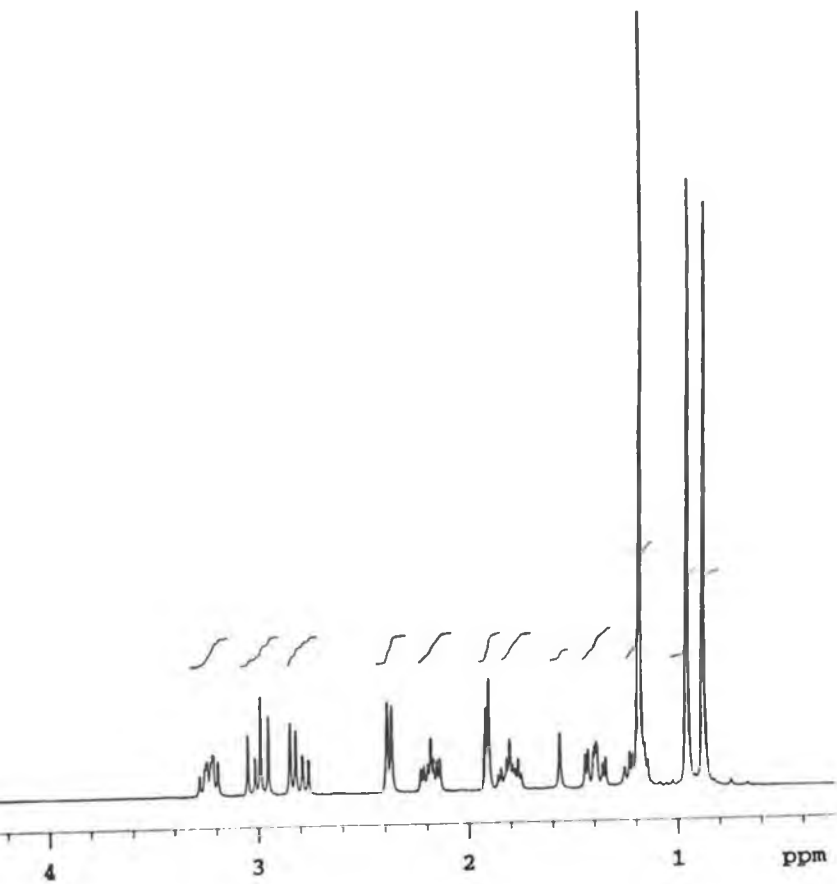
**31a**

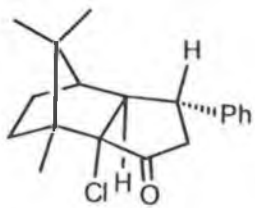

F2
(ppm)
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8
F1 (ppm)




**31b**



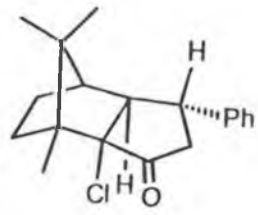

4
3
2
1
ppm



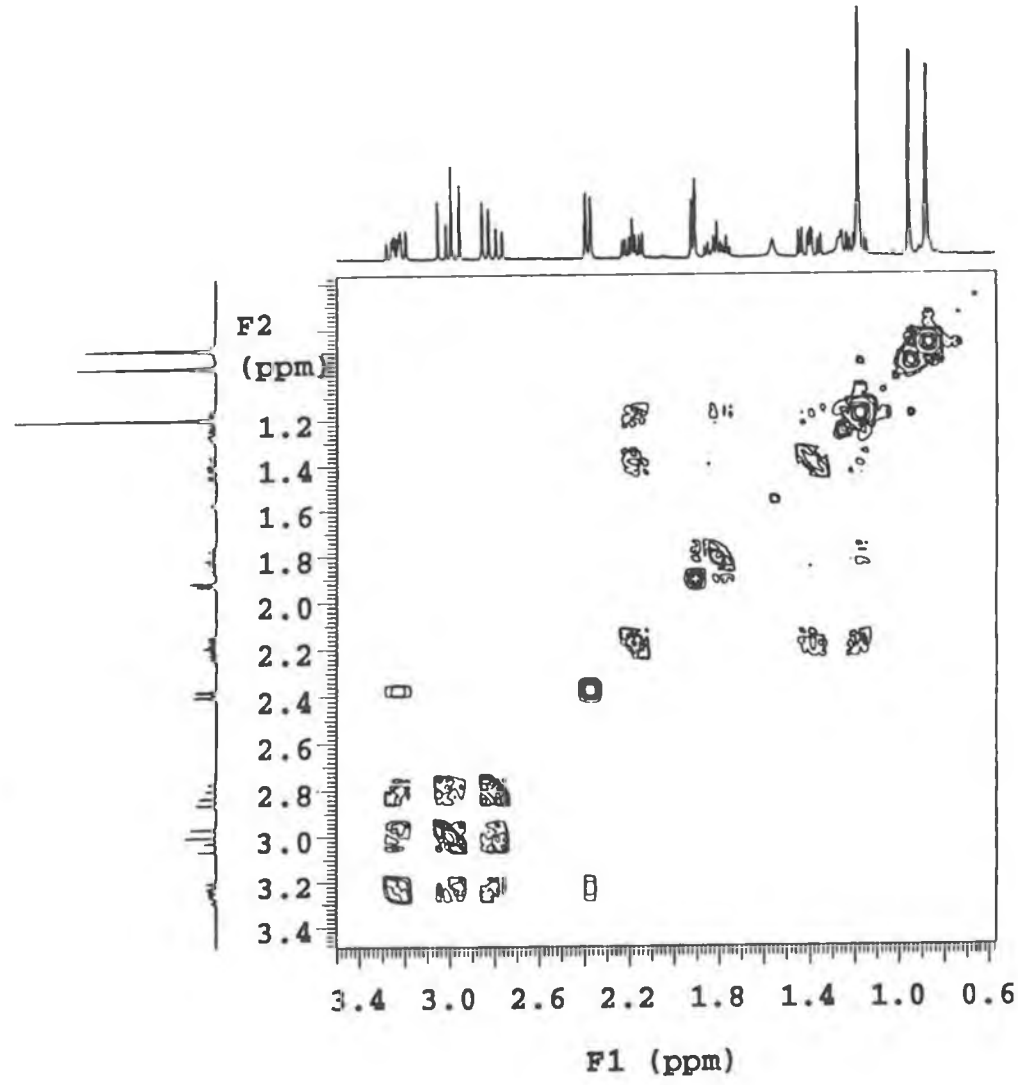

**31b**

60
40
20
0
ppm

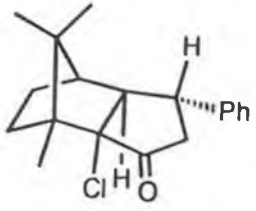
COSY of


H
Ph
Cl
H
O

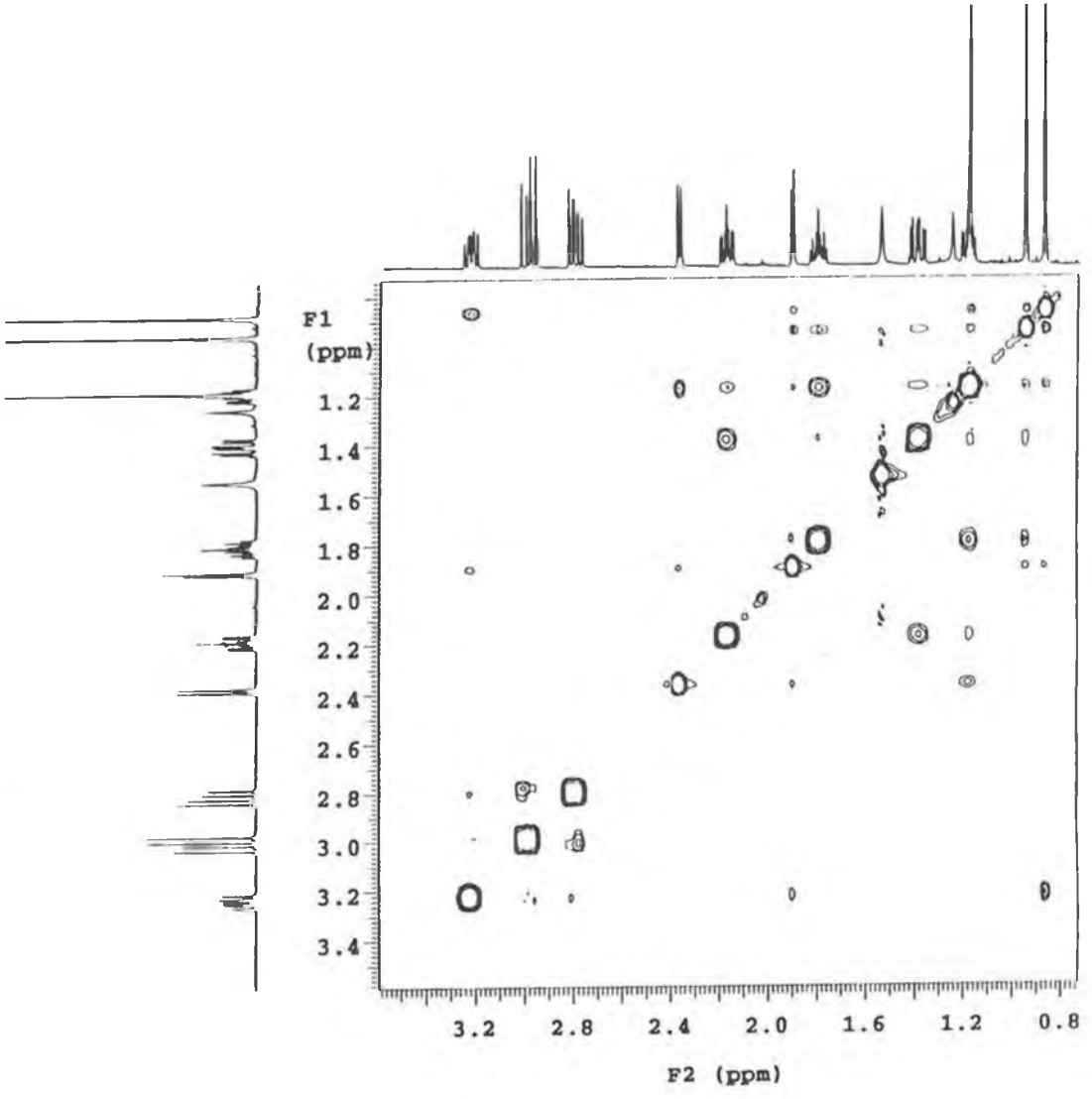
31b

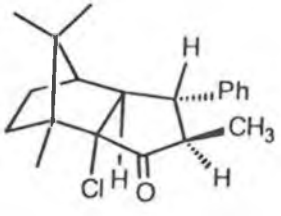

F2
(ppm)
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.4
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)

**NOESY of**

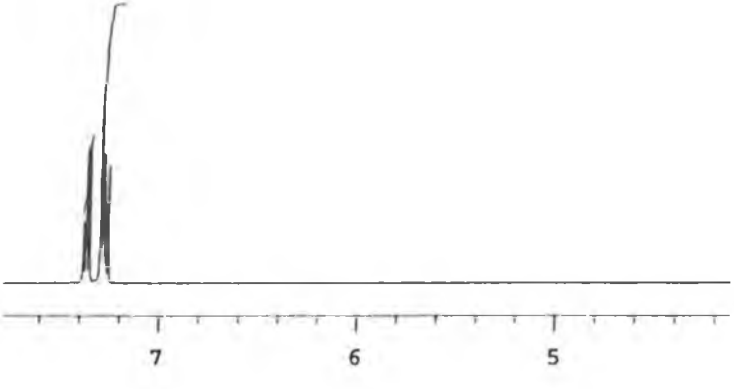

H
Ph
Cl
H
O

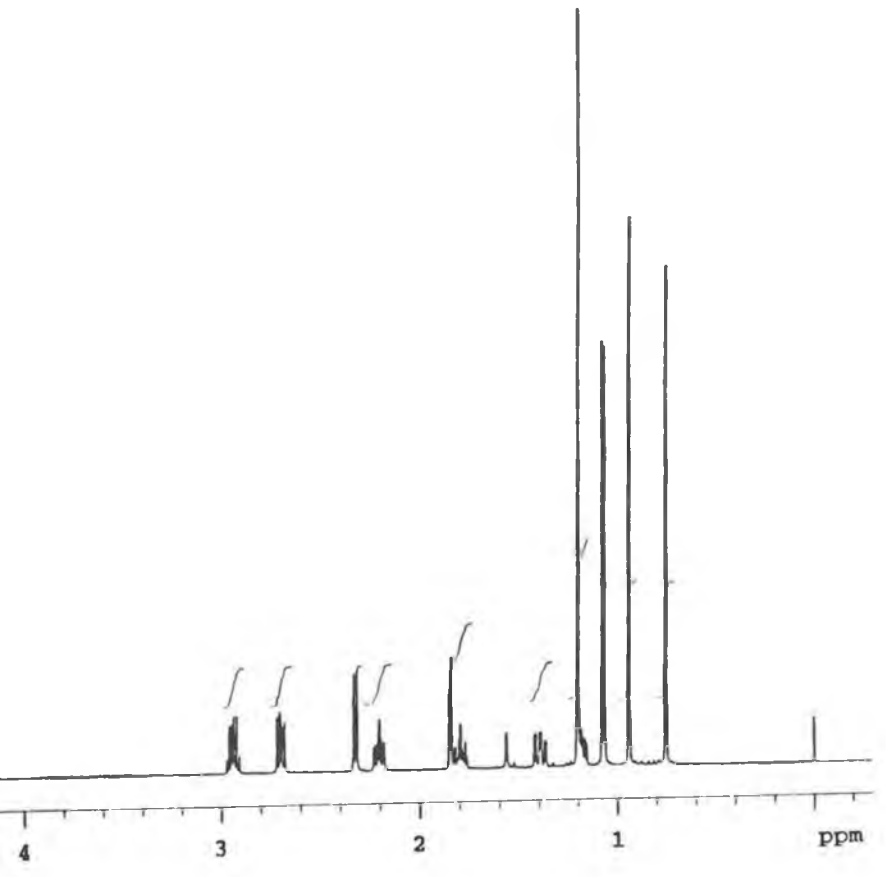
**31b**

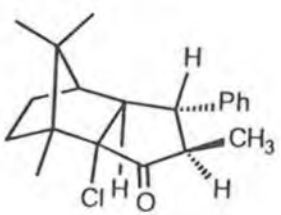

F1
(ppm)
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.2
2.8
2.4
2.0
1.6
1.2
0.8
F2 (ppm)



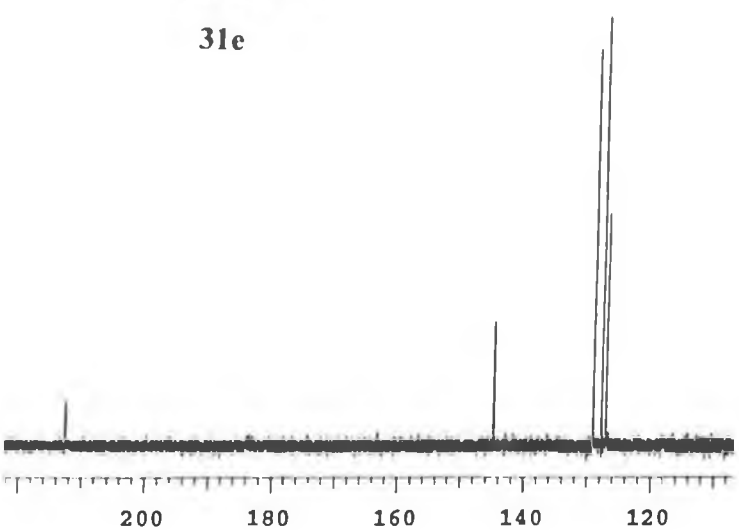

**31e**

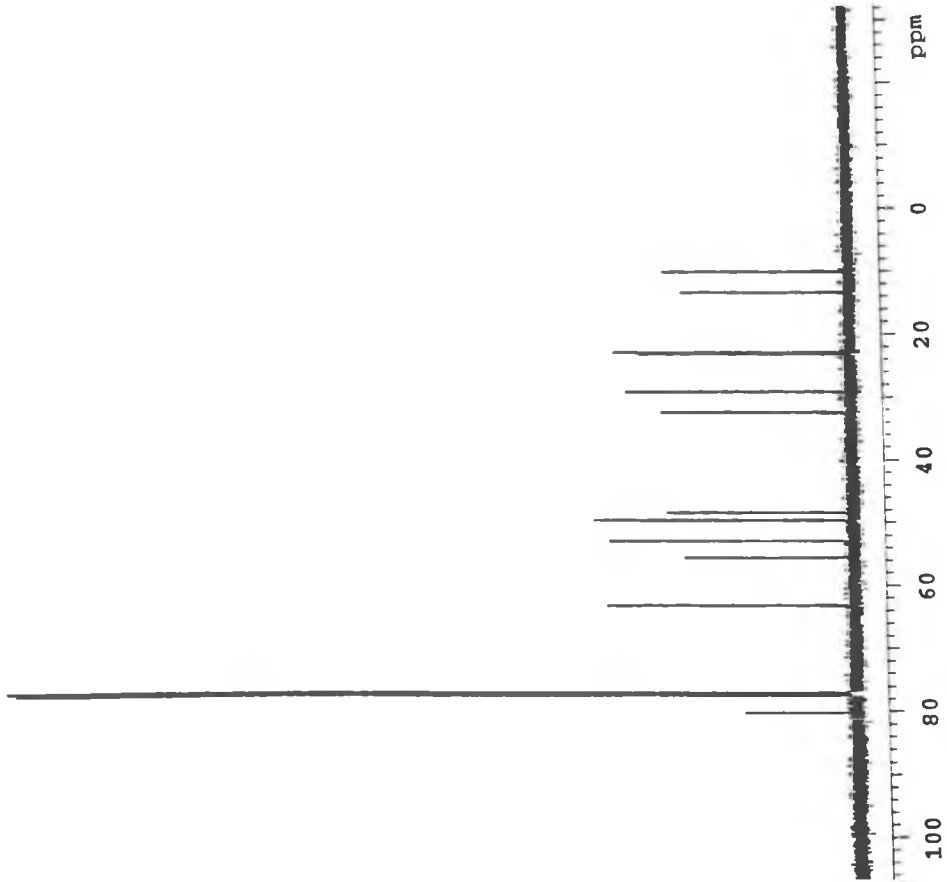


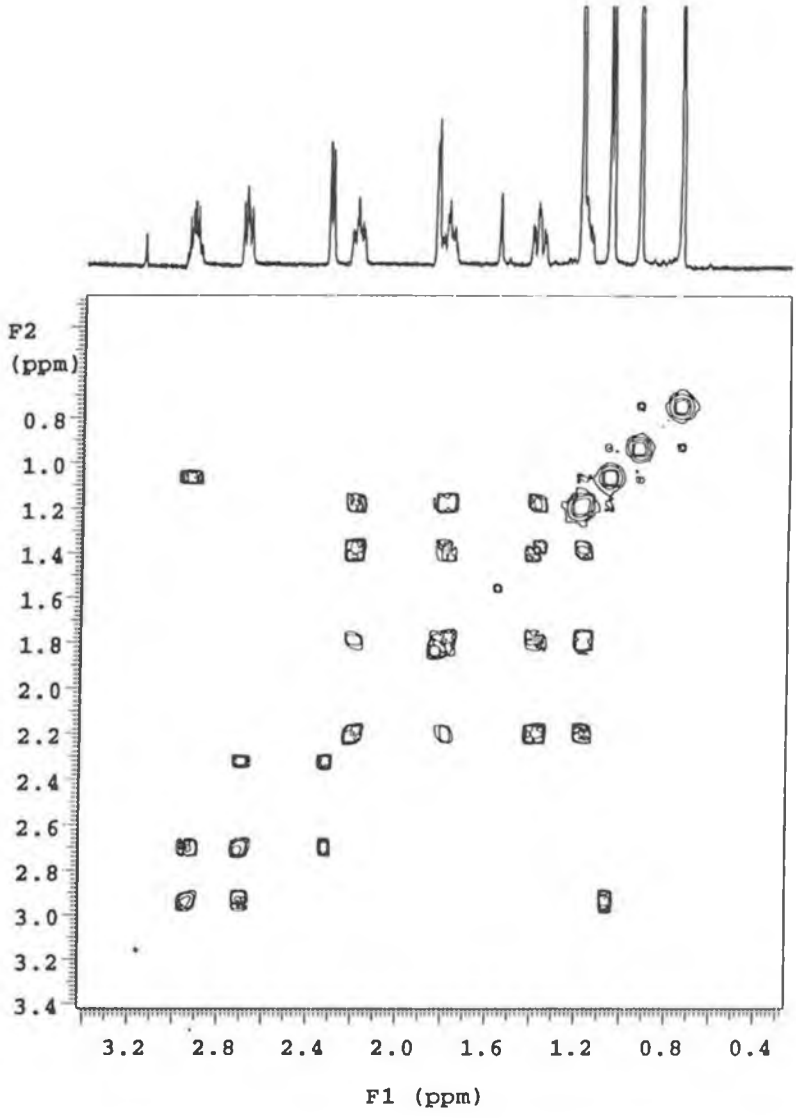

4
3
2
1
ppm



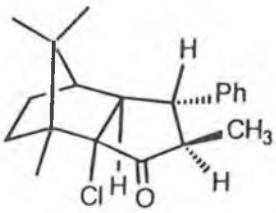

**31e**



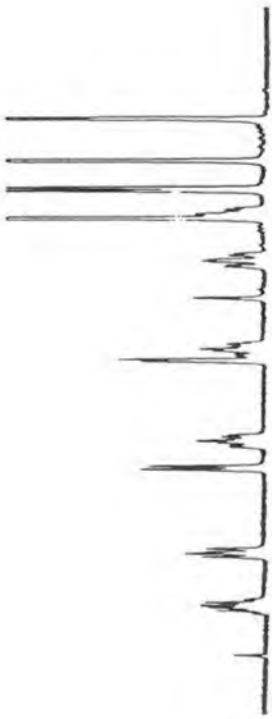

ppm
0
20
40
60
80
100


F2
(ppm)
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
F1 (ppm)

**COSY of**

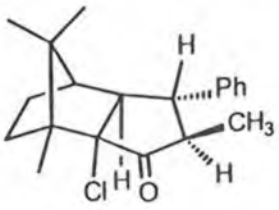



**31e**

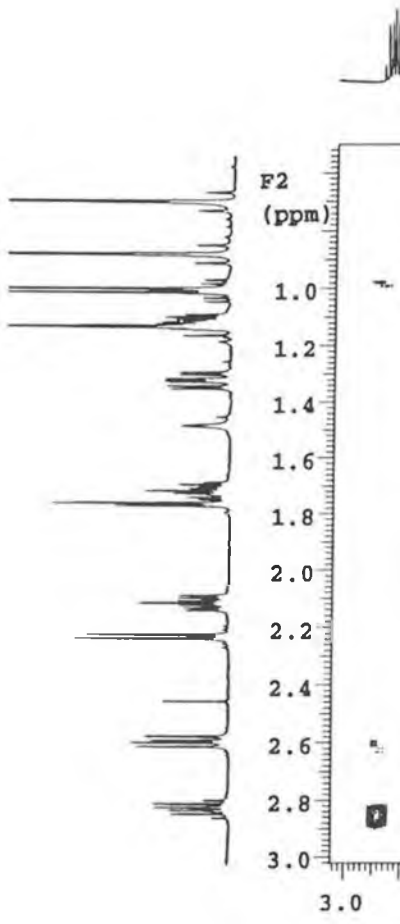


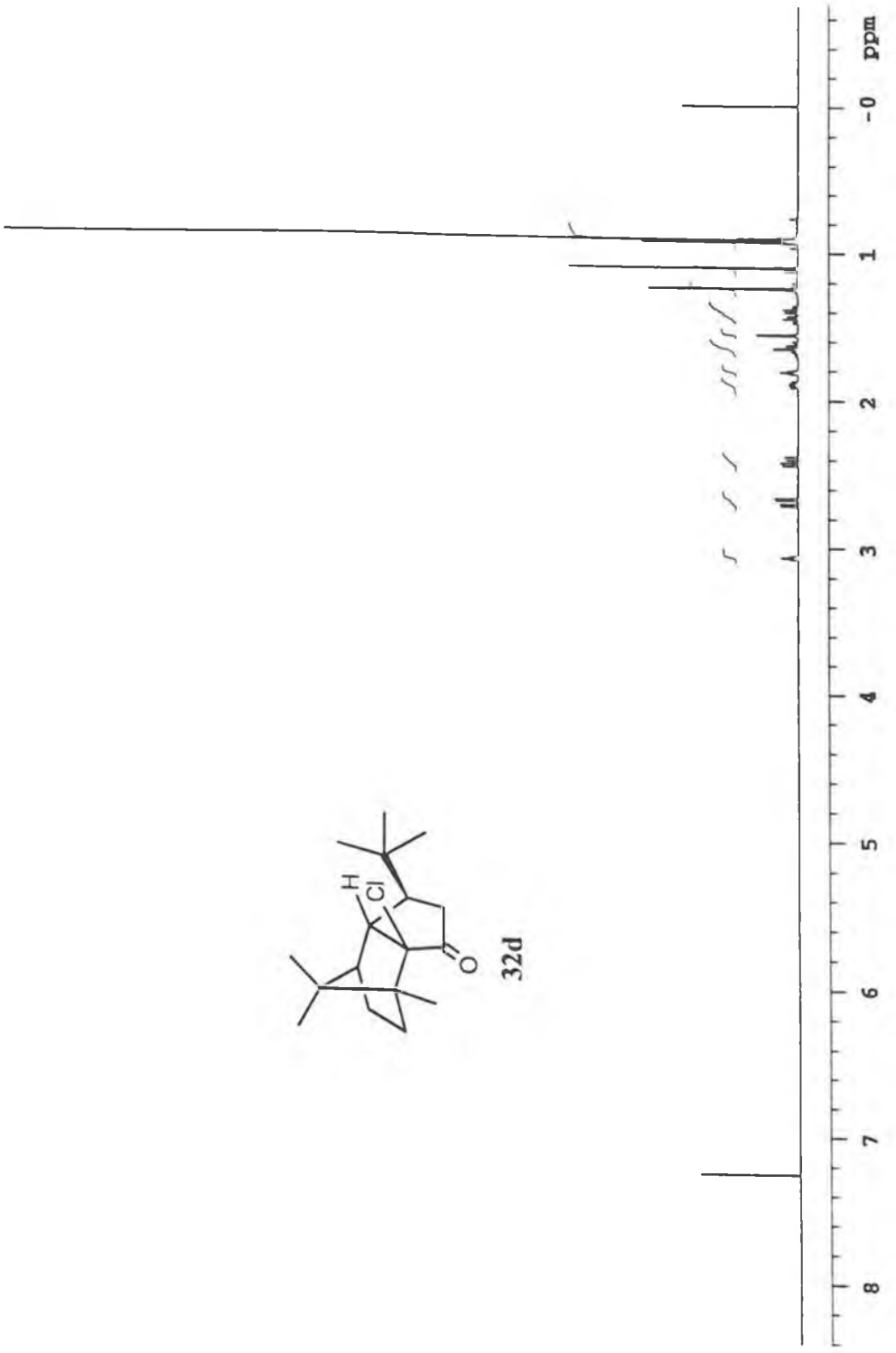
F1 (ppm)
2.6
2.2
1.8
1.4
1.0
0.6

**NOESY of**

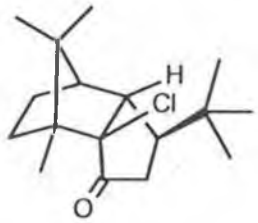



**31e**





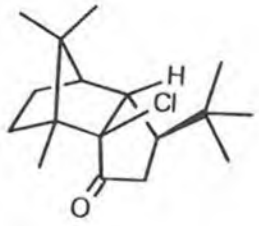

**32d**



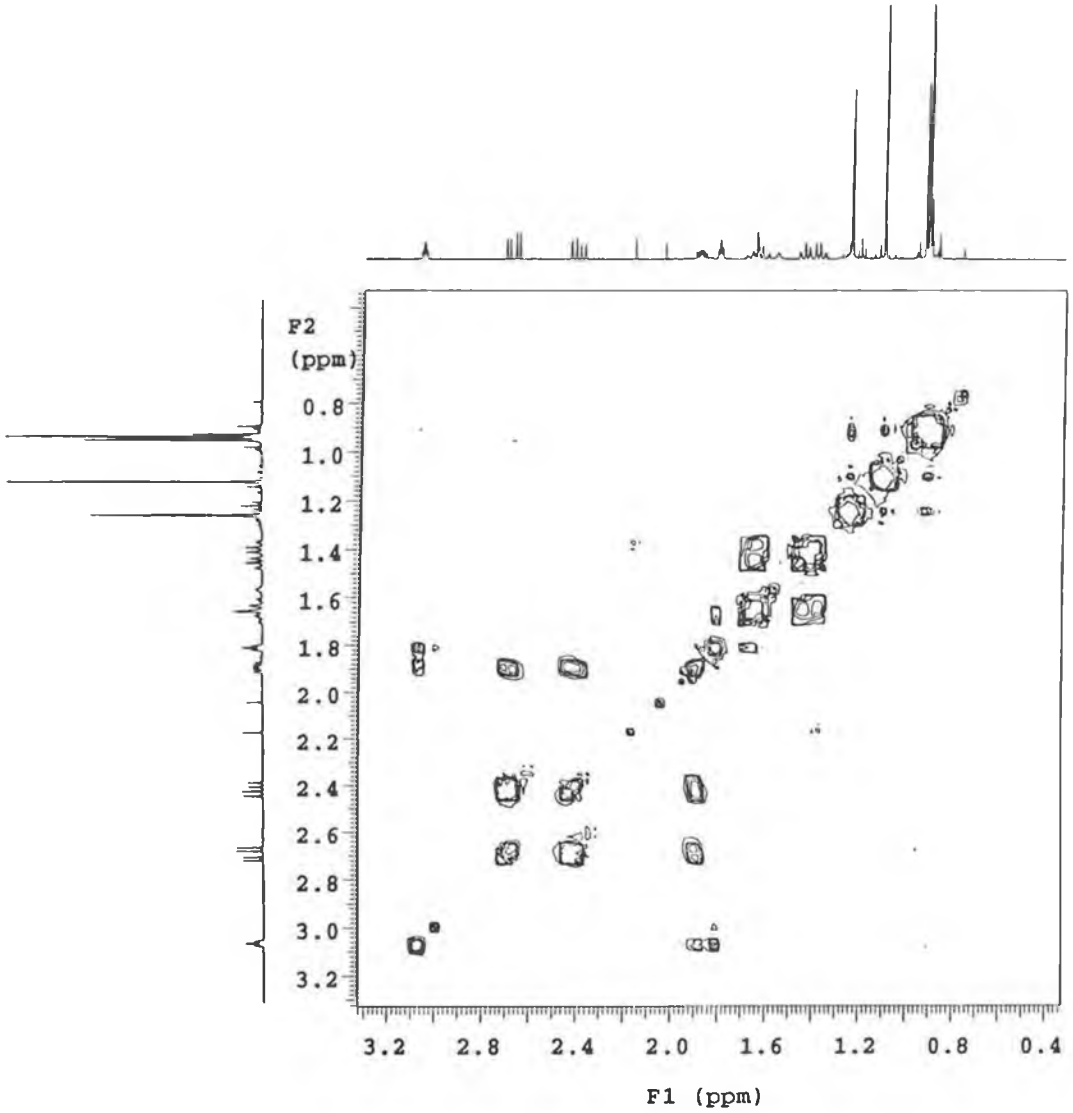

**32d**

60
40
20
0
ppm

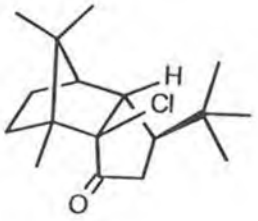
**COSY of**


H
Cl
O

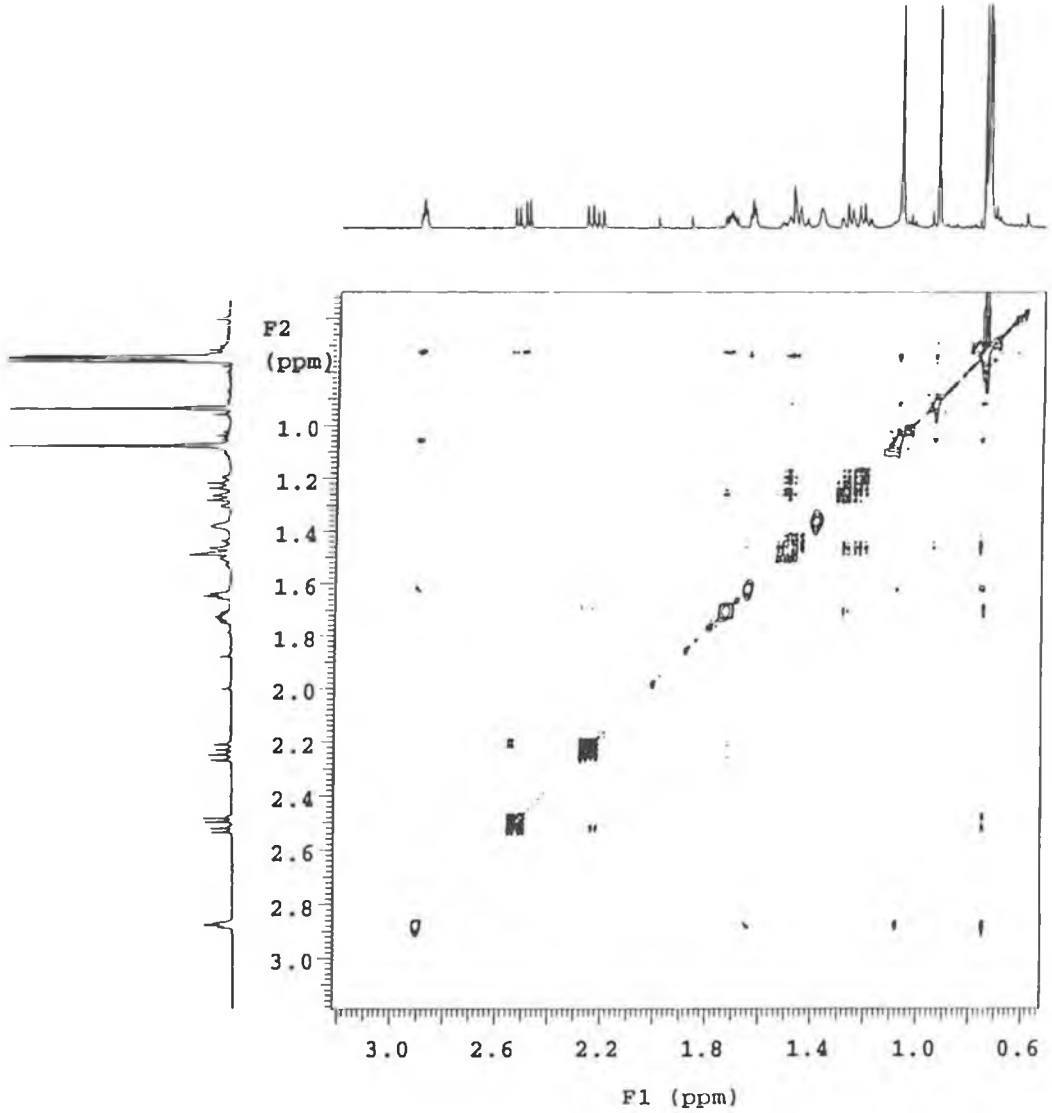
**32d**

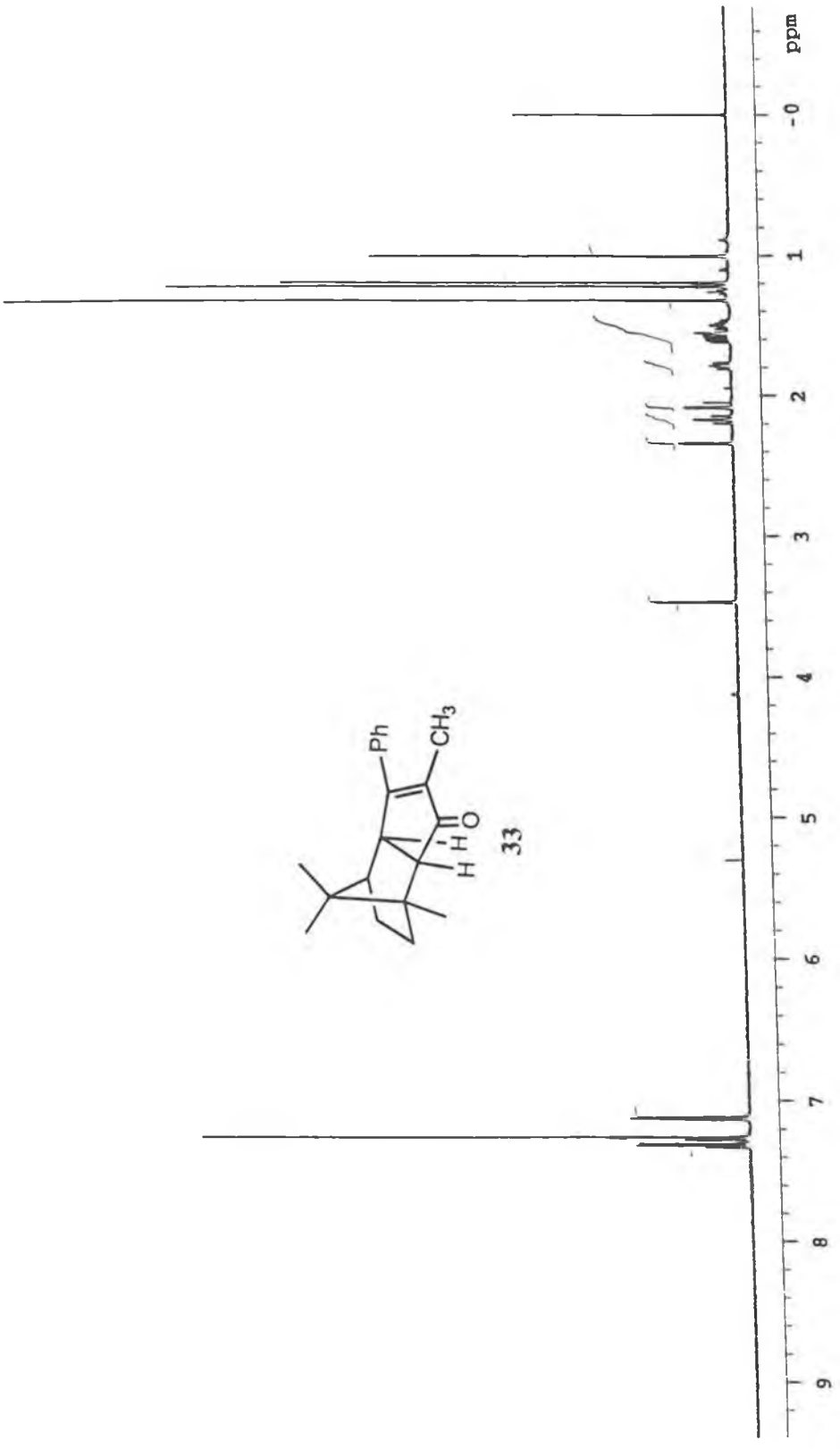

F2
(ppm)
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.2
2.8
2.4
2.0
1.6
1.2
0.8
0.4
F1 (ppm)

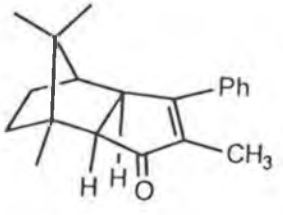
**NOESY of**


H
Cl
O

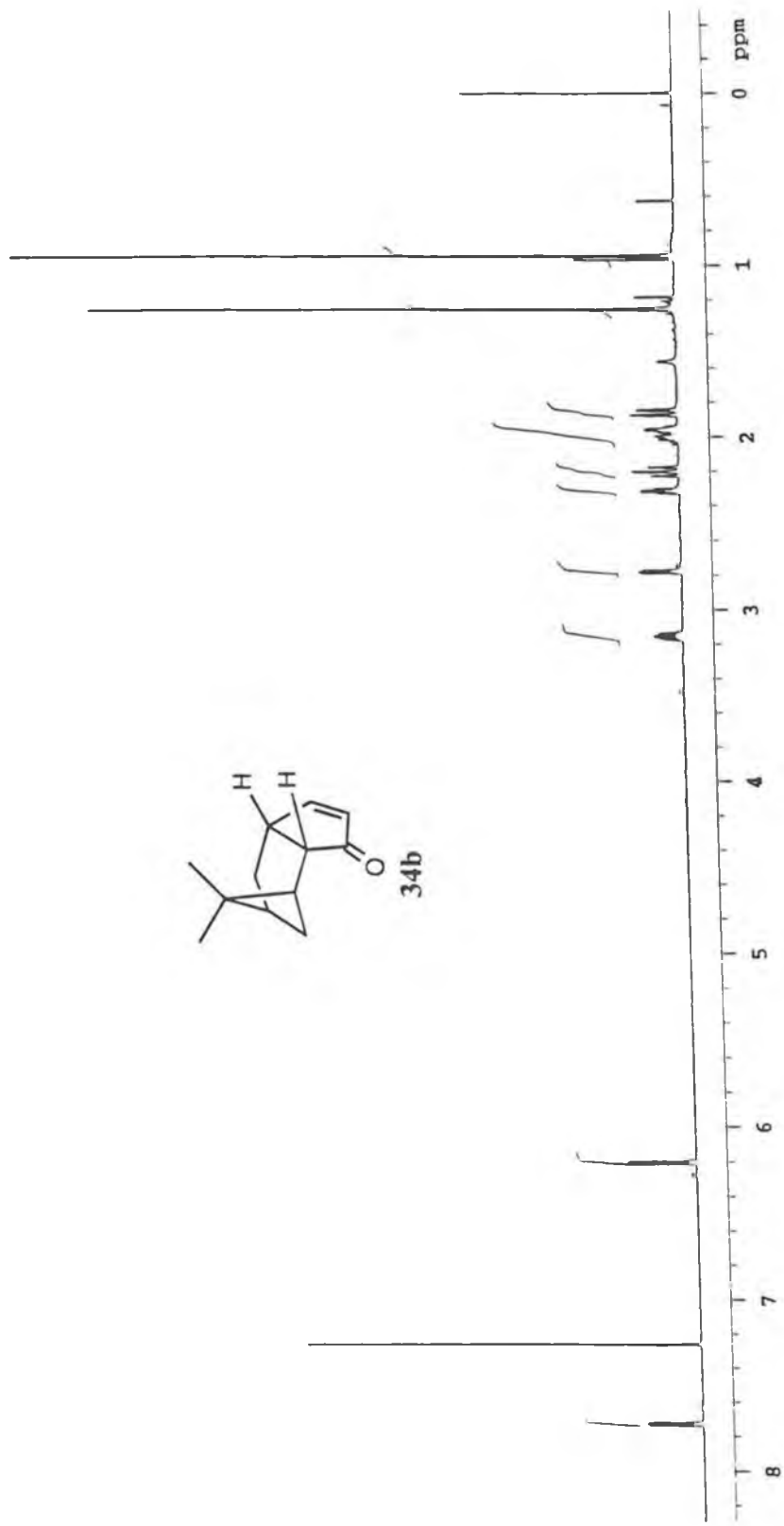
**32d**


F2
(ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)

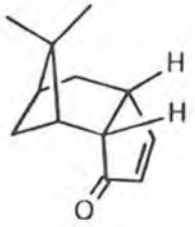

Ph
CH3
H
H
O
33
ppm
9
8
7
6
5
4
3
2
1
-0



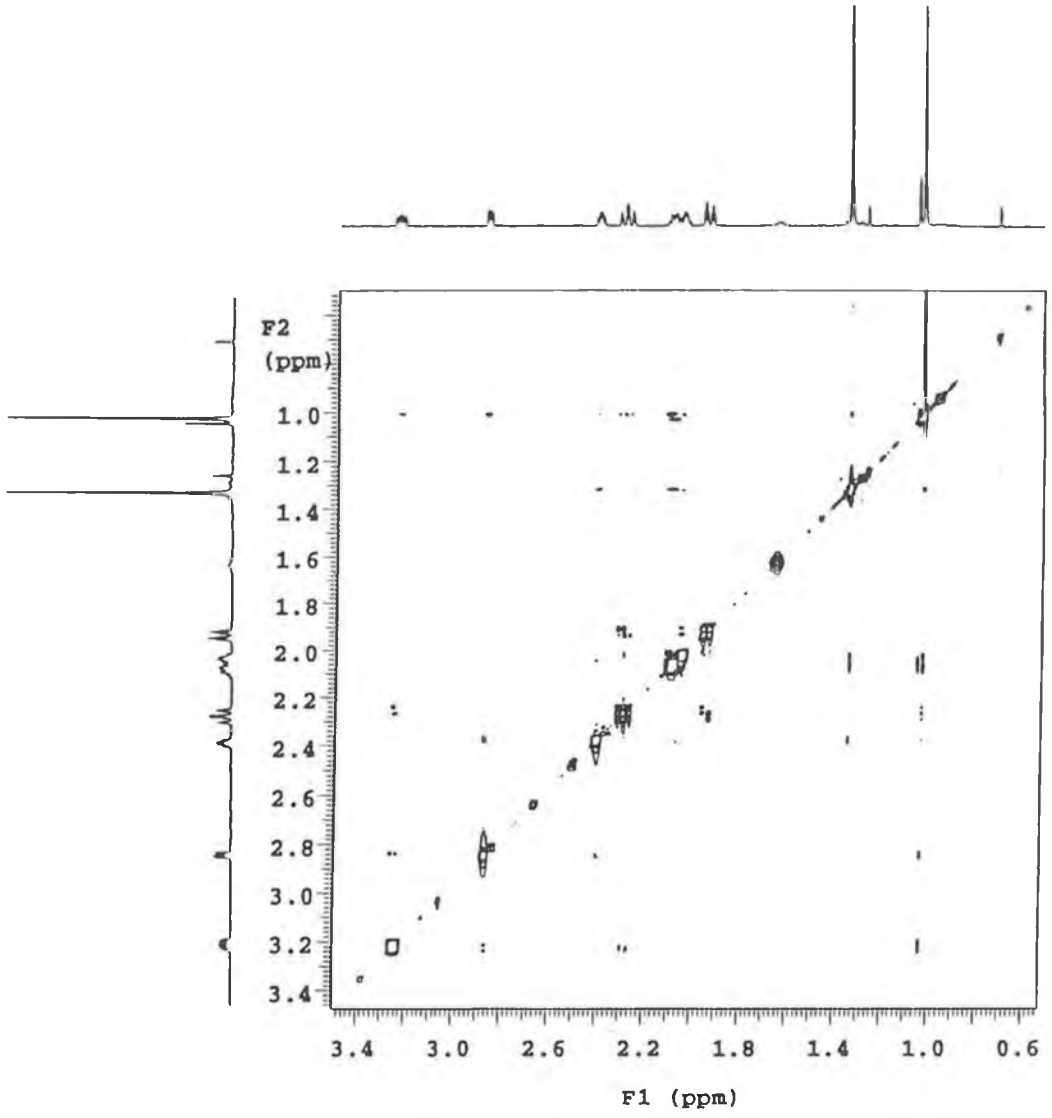

**33**


H
H
O
34b
0
1
2
3
4
5
6
7
8
ppm

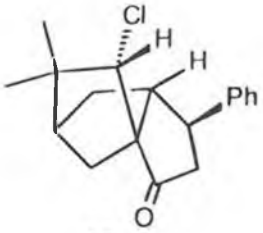
NOESY of


H
H
O

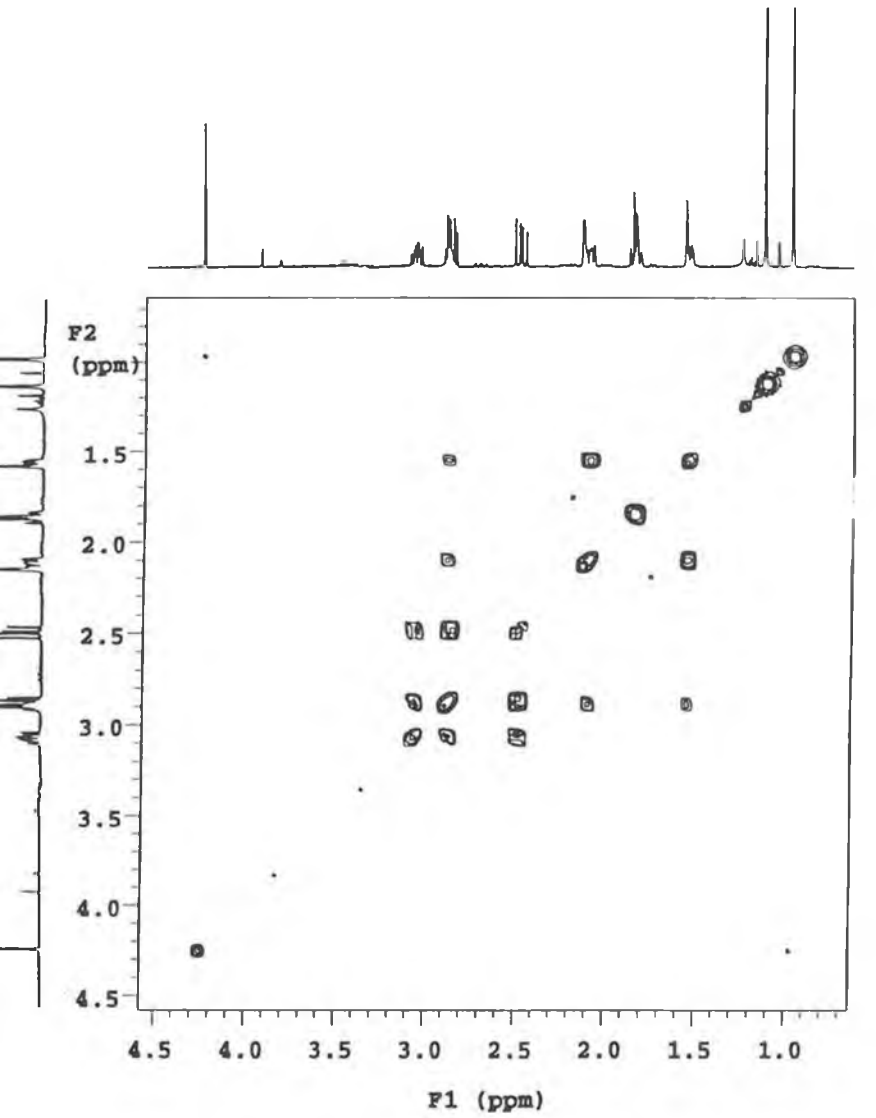
**34b**


F2
(ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.4
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)

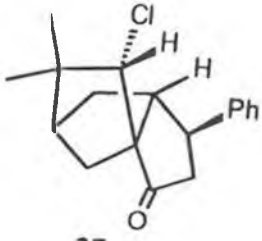
**COSY of**



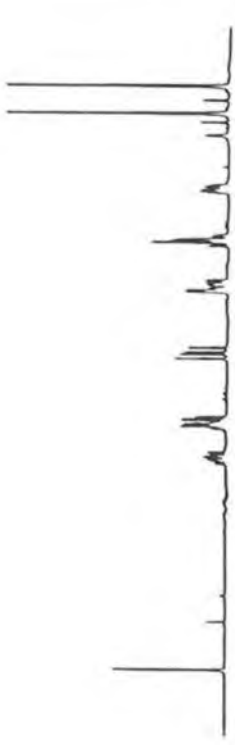

**37**

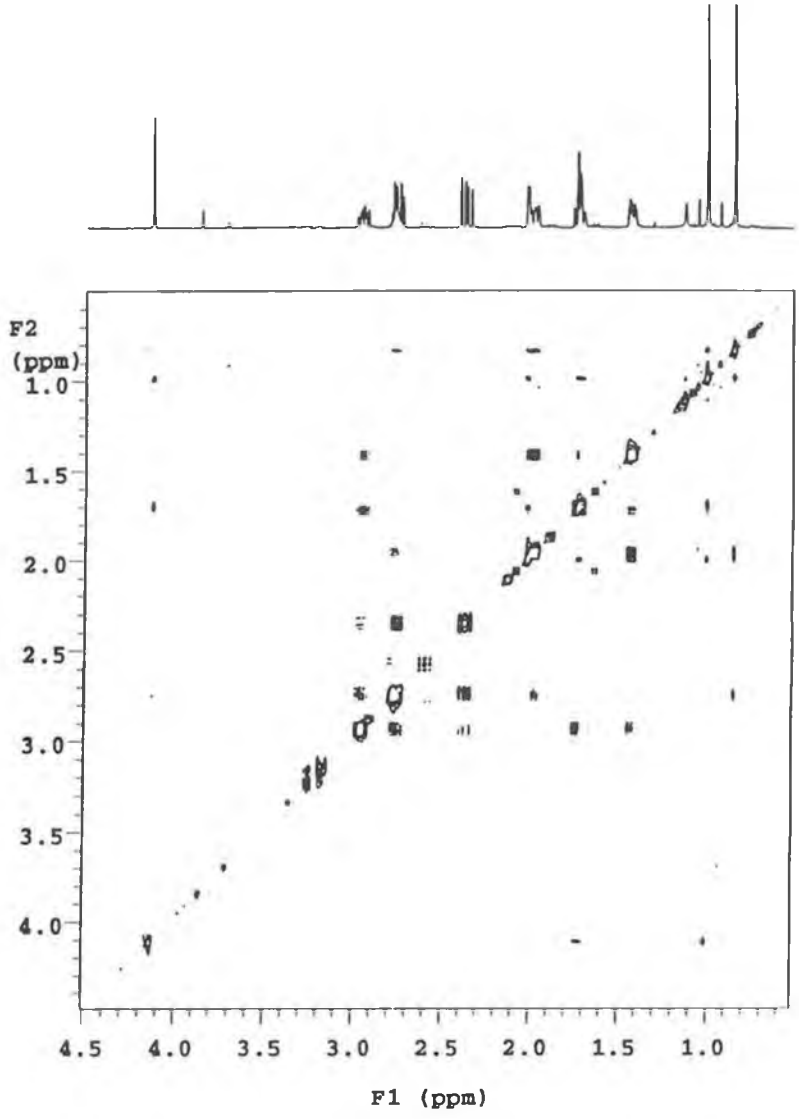

F2
(ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

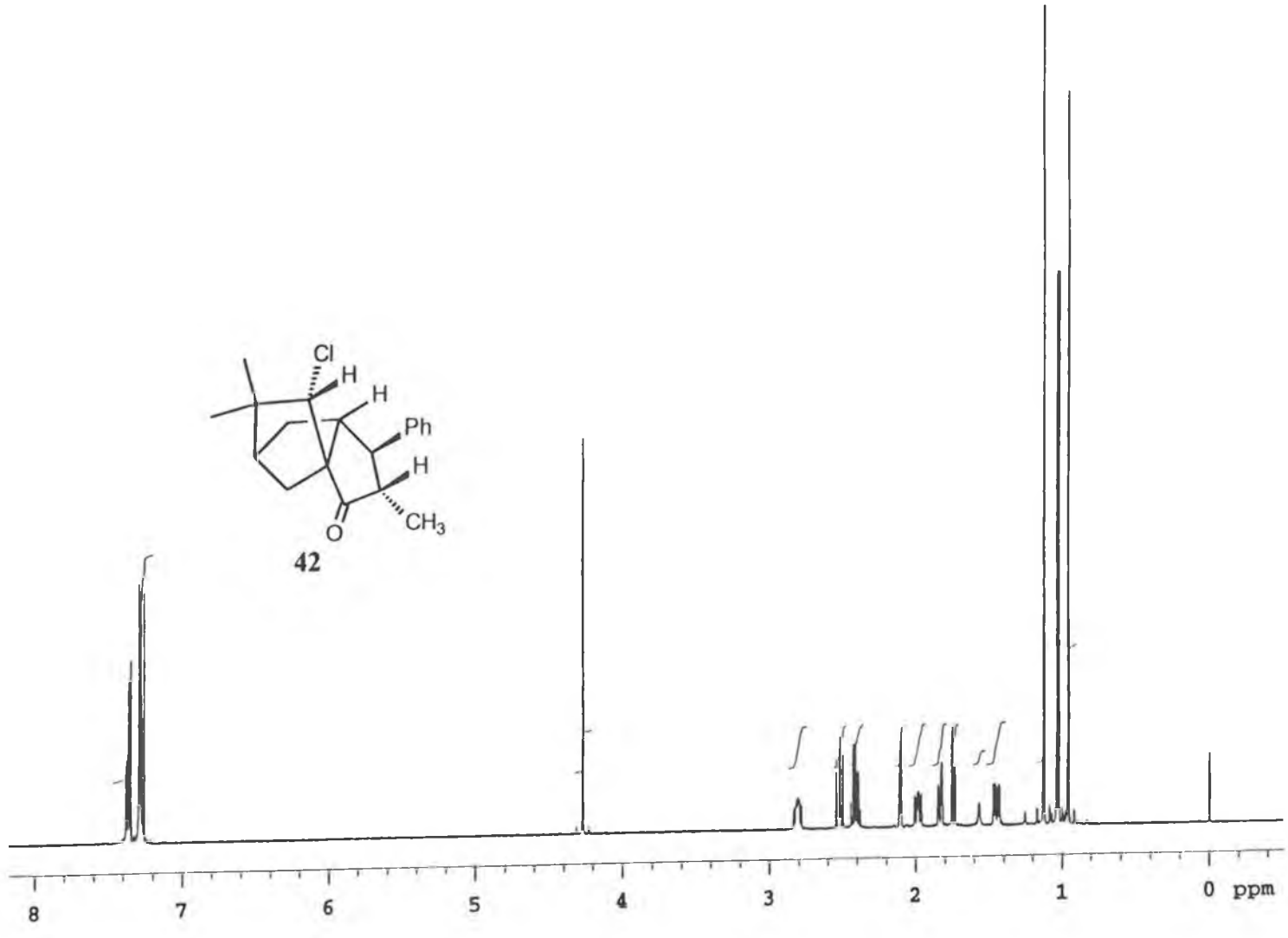
**NOESY of**



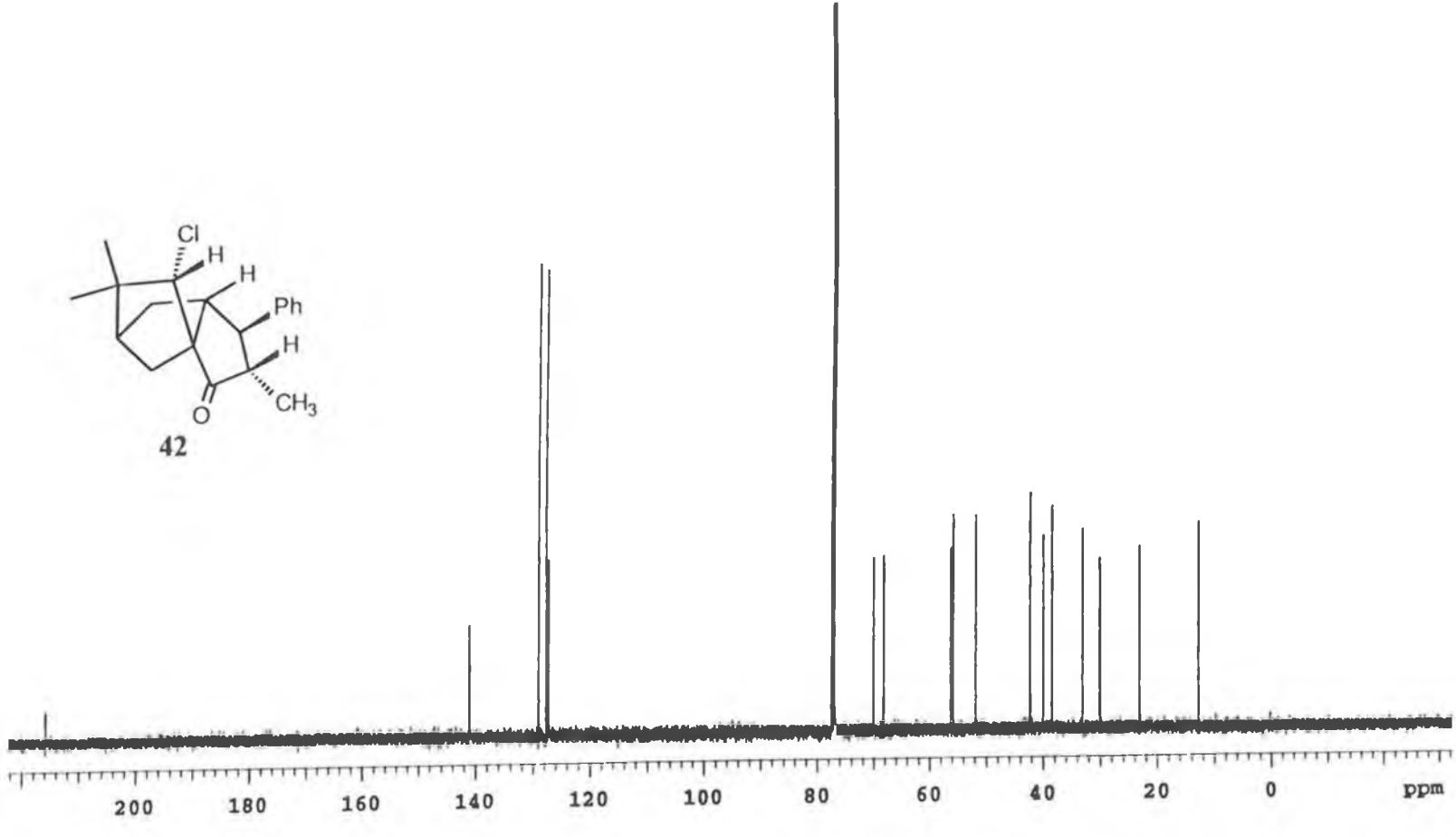

**37**




F2
(ppm)
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)

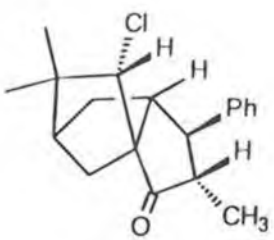



42

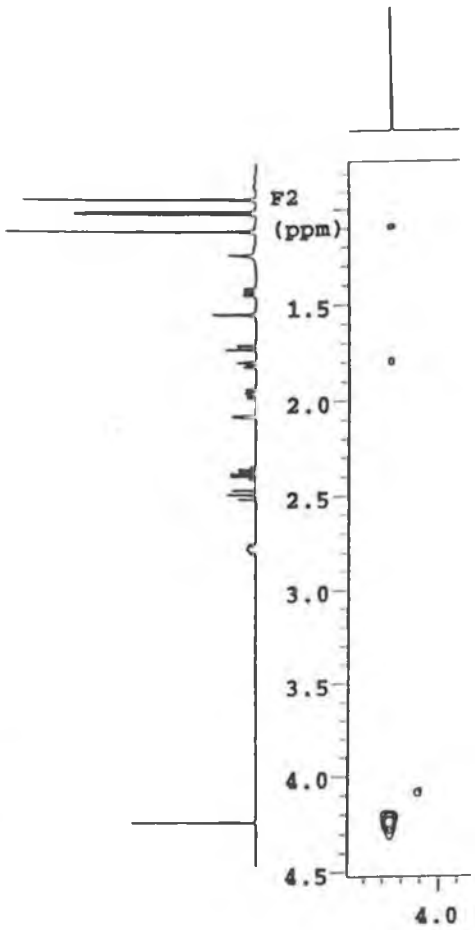



42

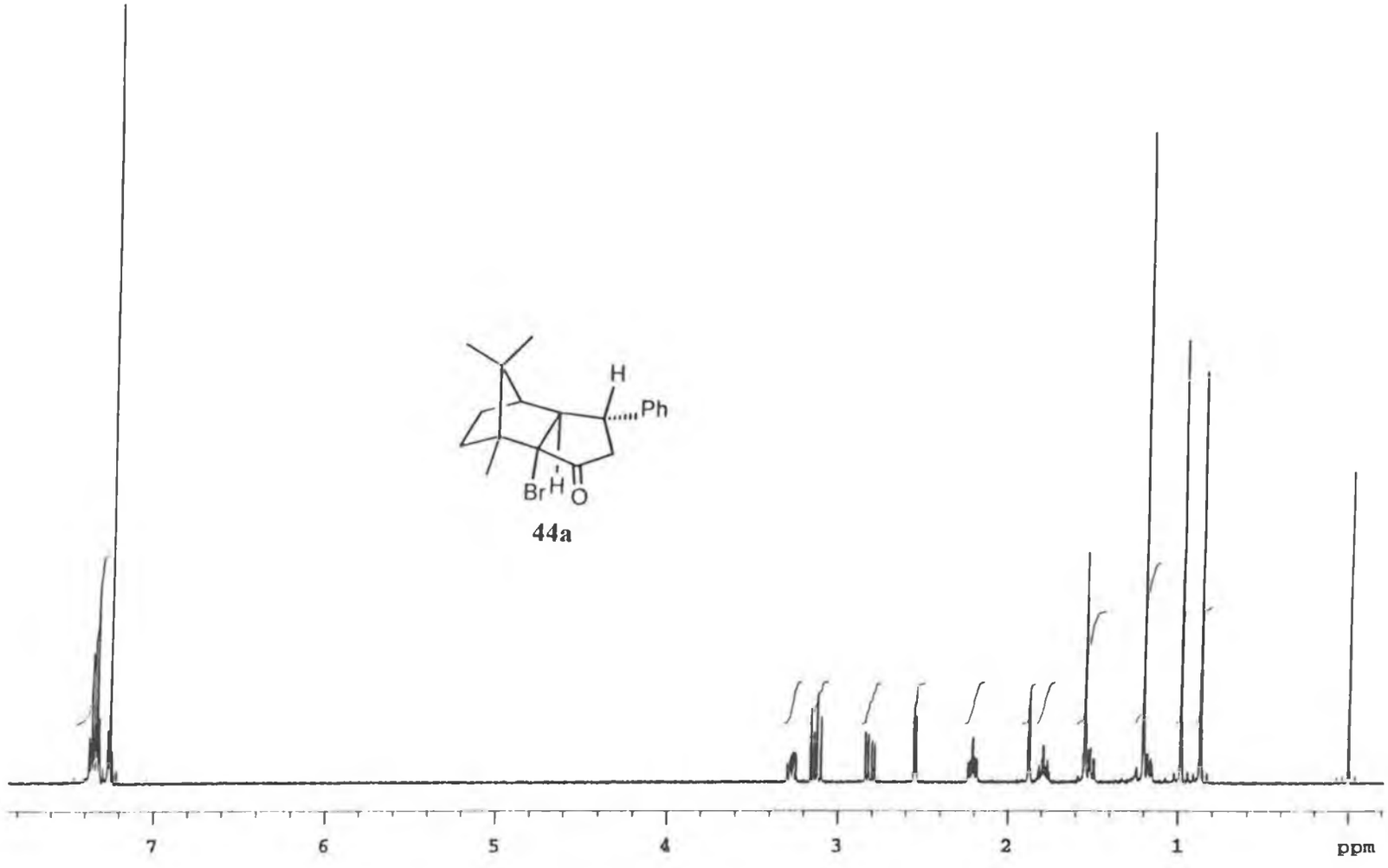
**NOESY of**



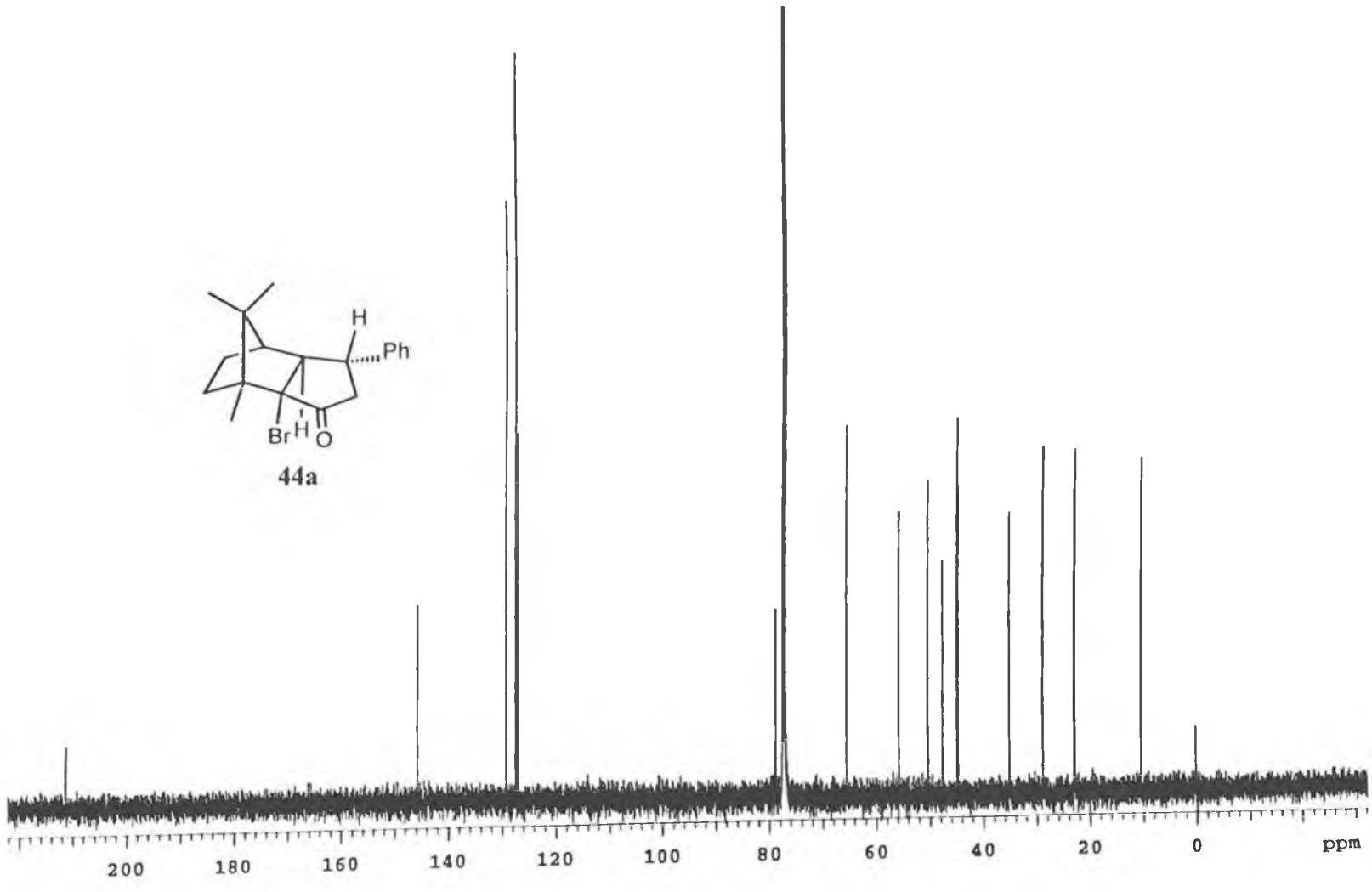

**42**



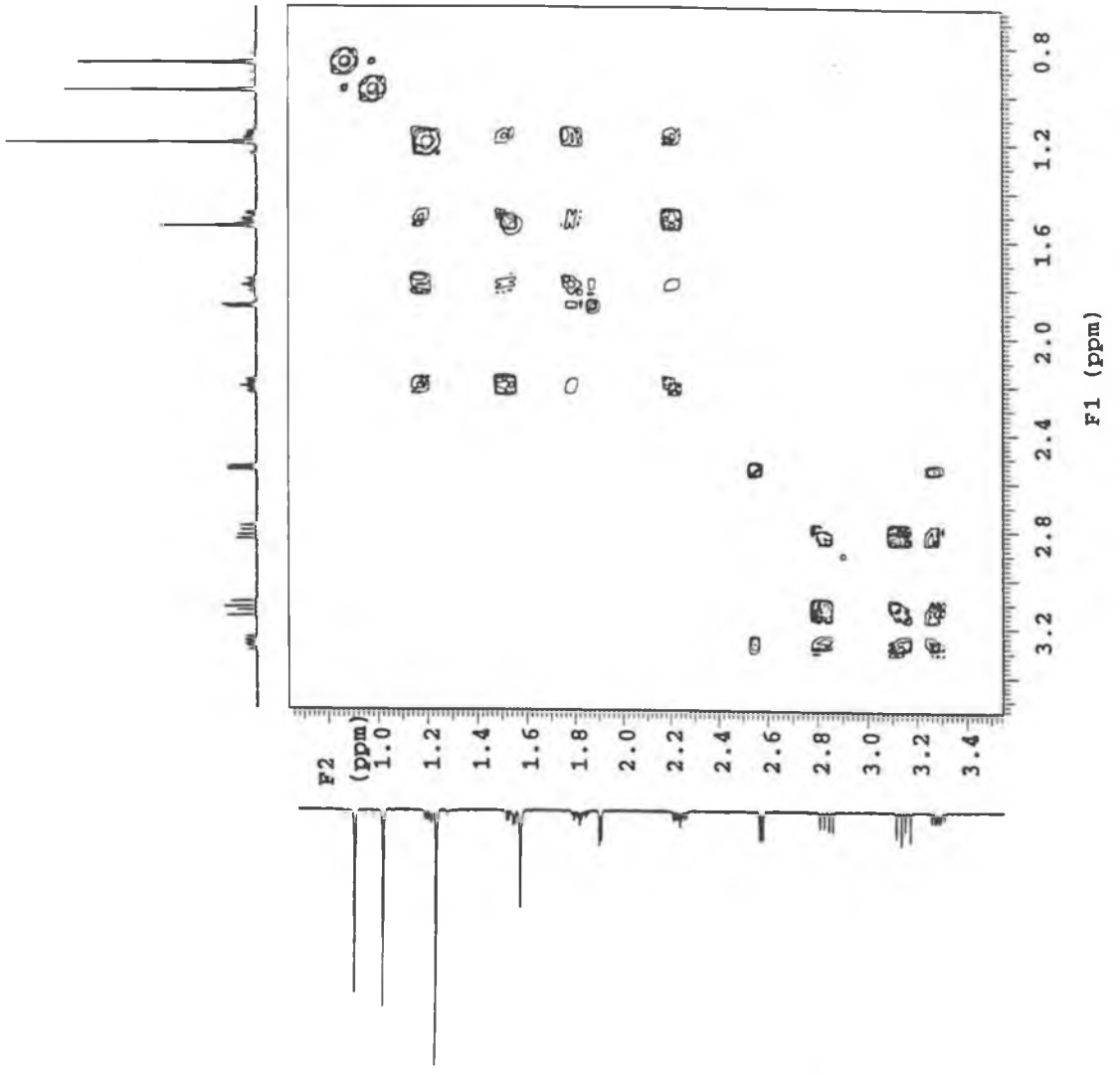
3.5
3.0
2.5
2.0
1.5
1.0
F1 (ppm)



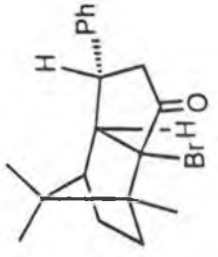

**44a**




**44a**

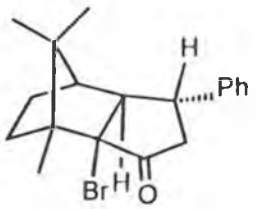

F2 (ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
F1 (ppm)
3.2
2.8
2.4
2.0
1.6
1.2
0.8

COSY of

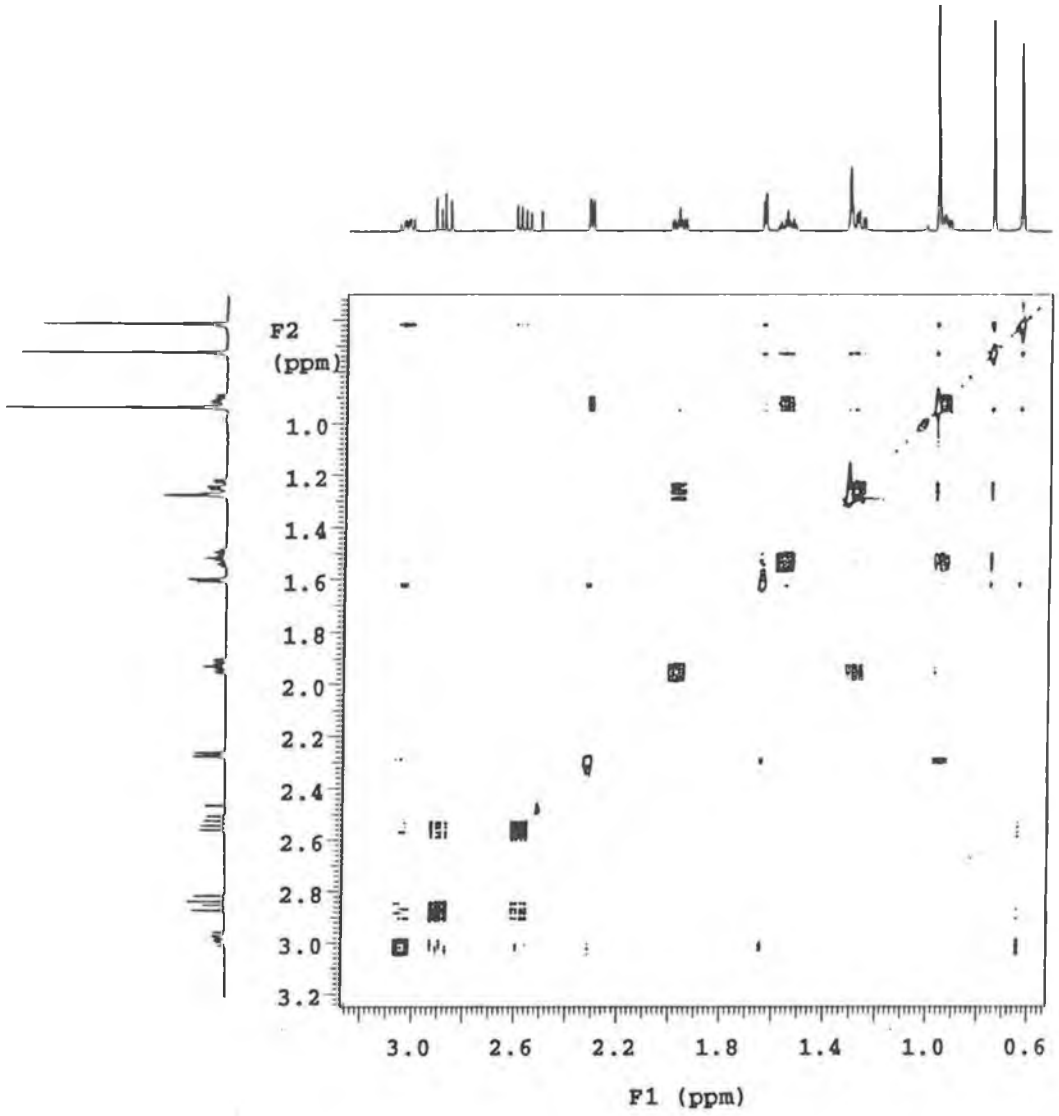

H
Ph
Br
H
O

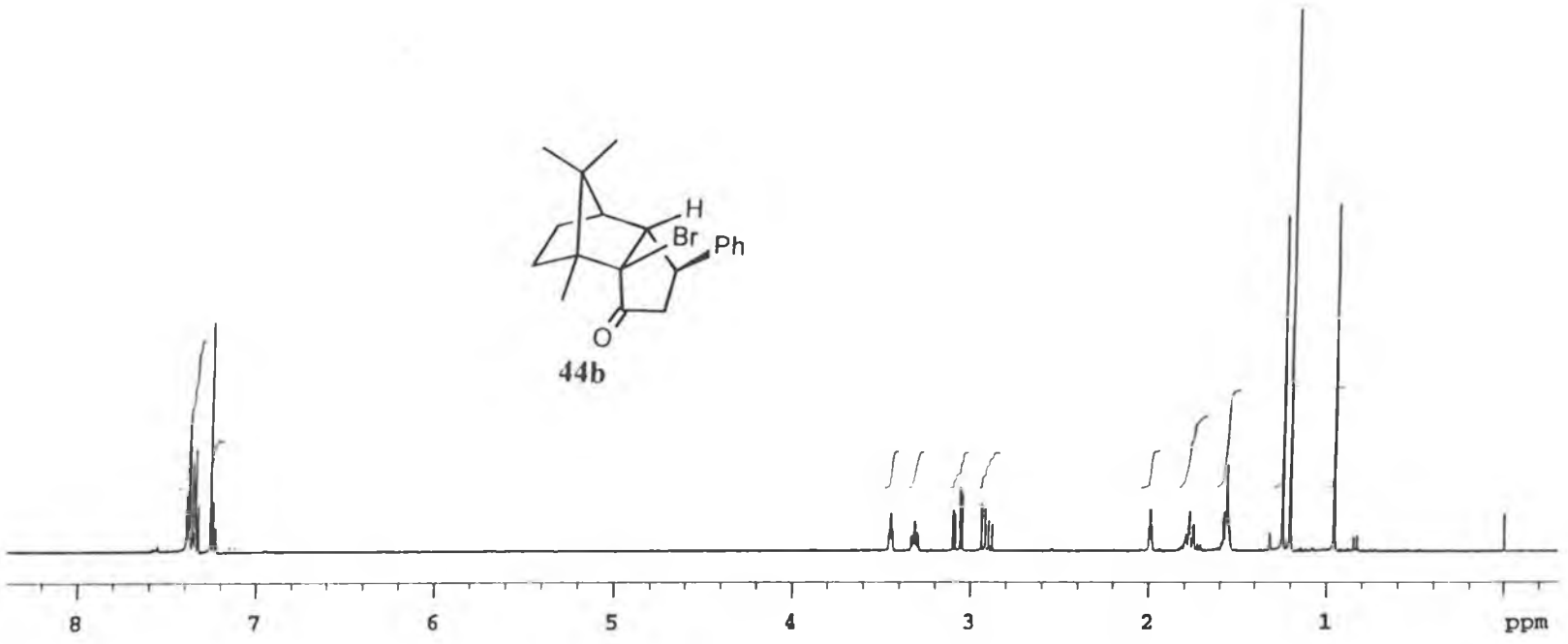
44a

**NOESY of**

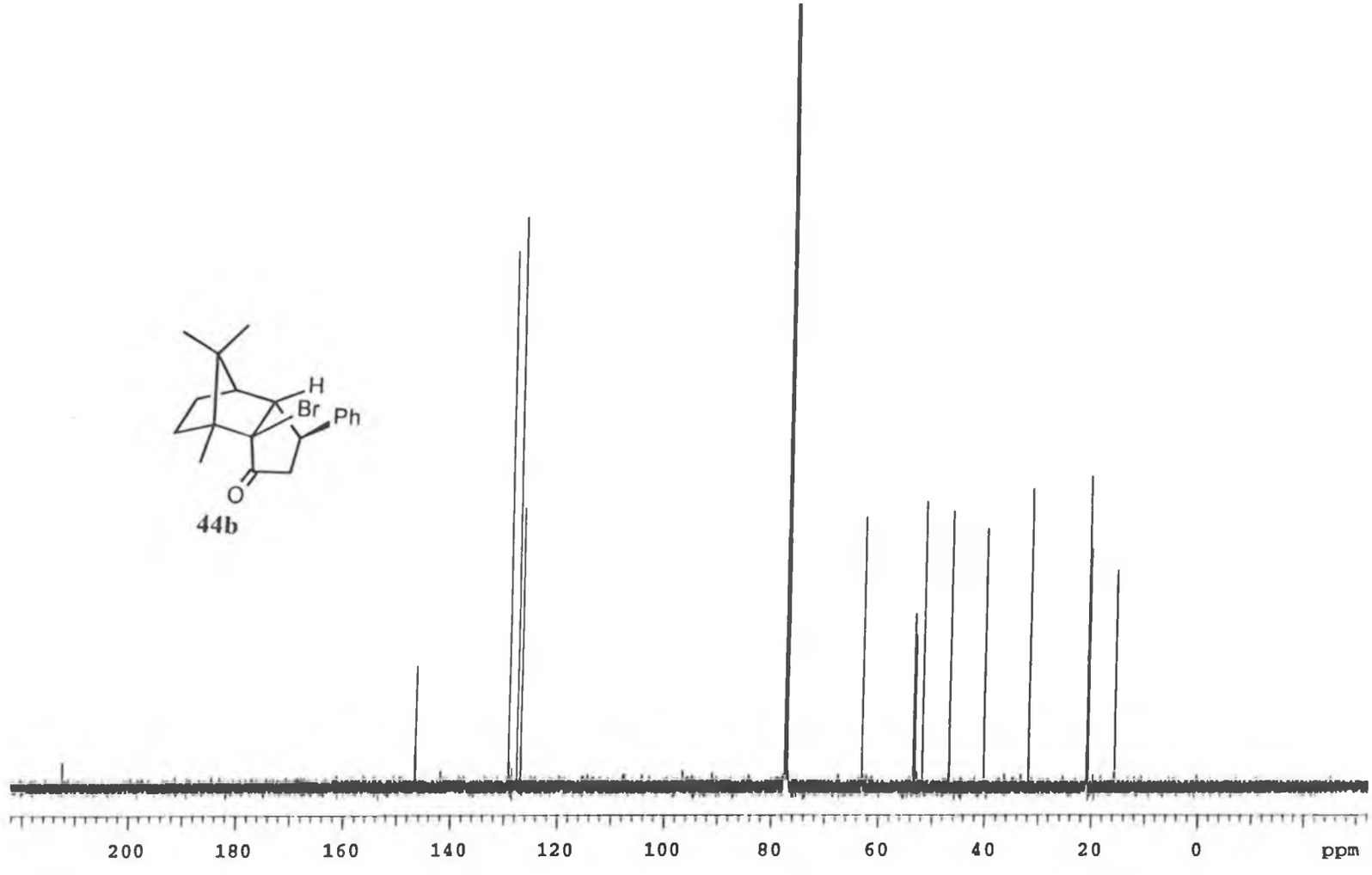

H
Ph
Br
H
O

**44a**


F2
(ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)

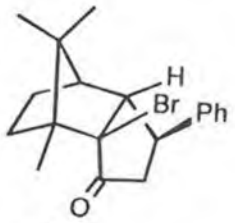



**44b**

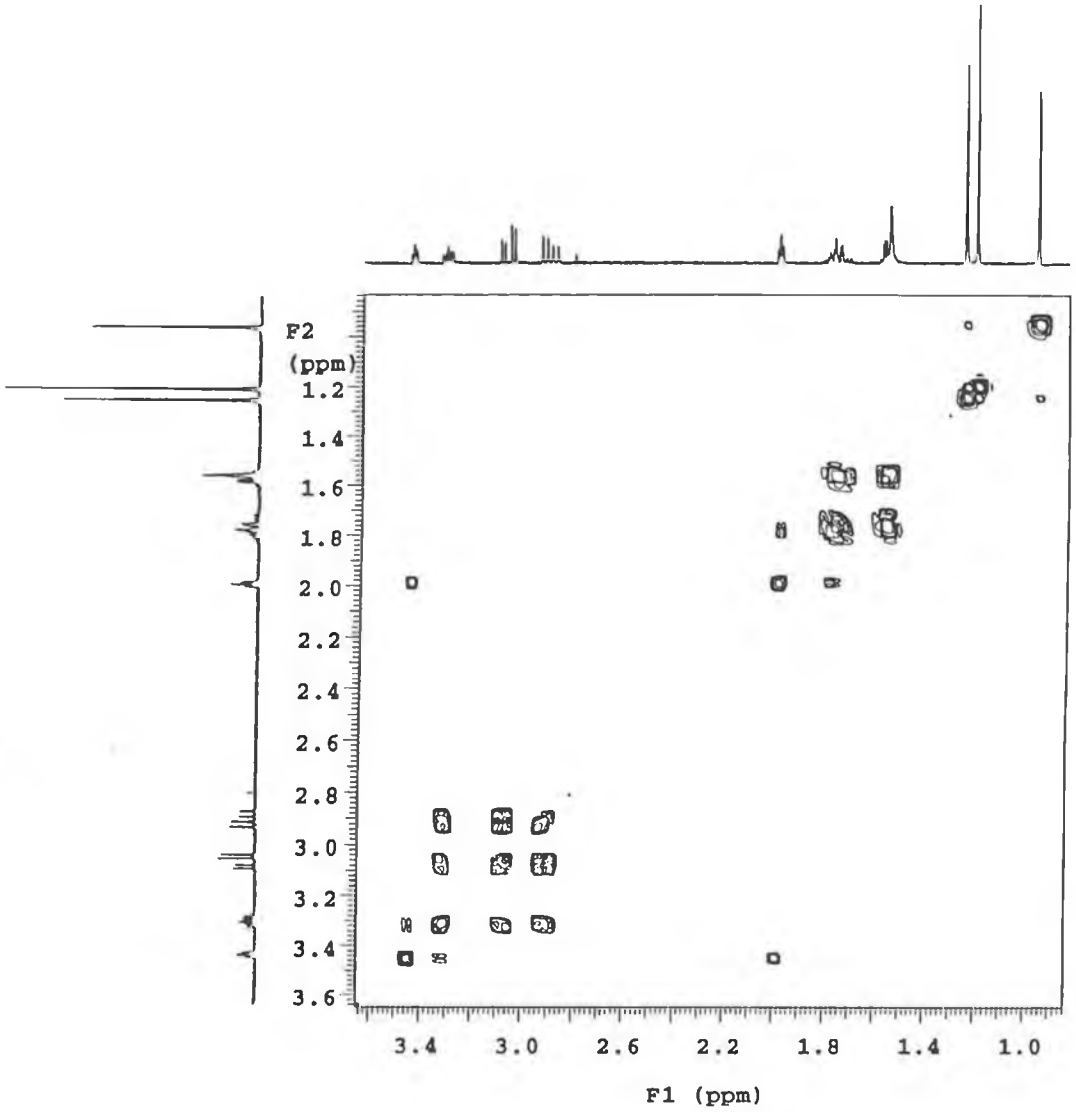



**44b**

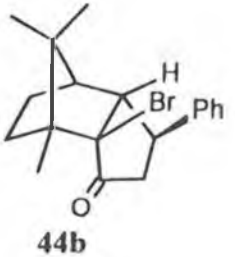
**COSY of**


H
Br
Ph
O

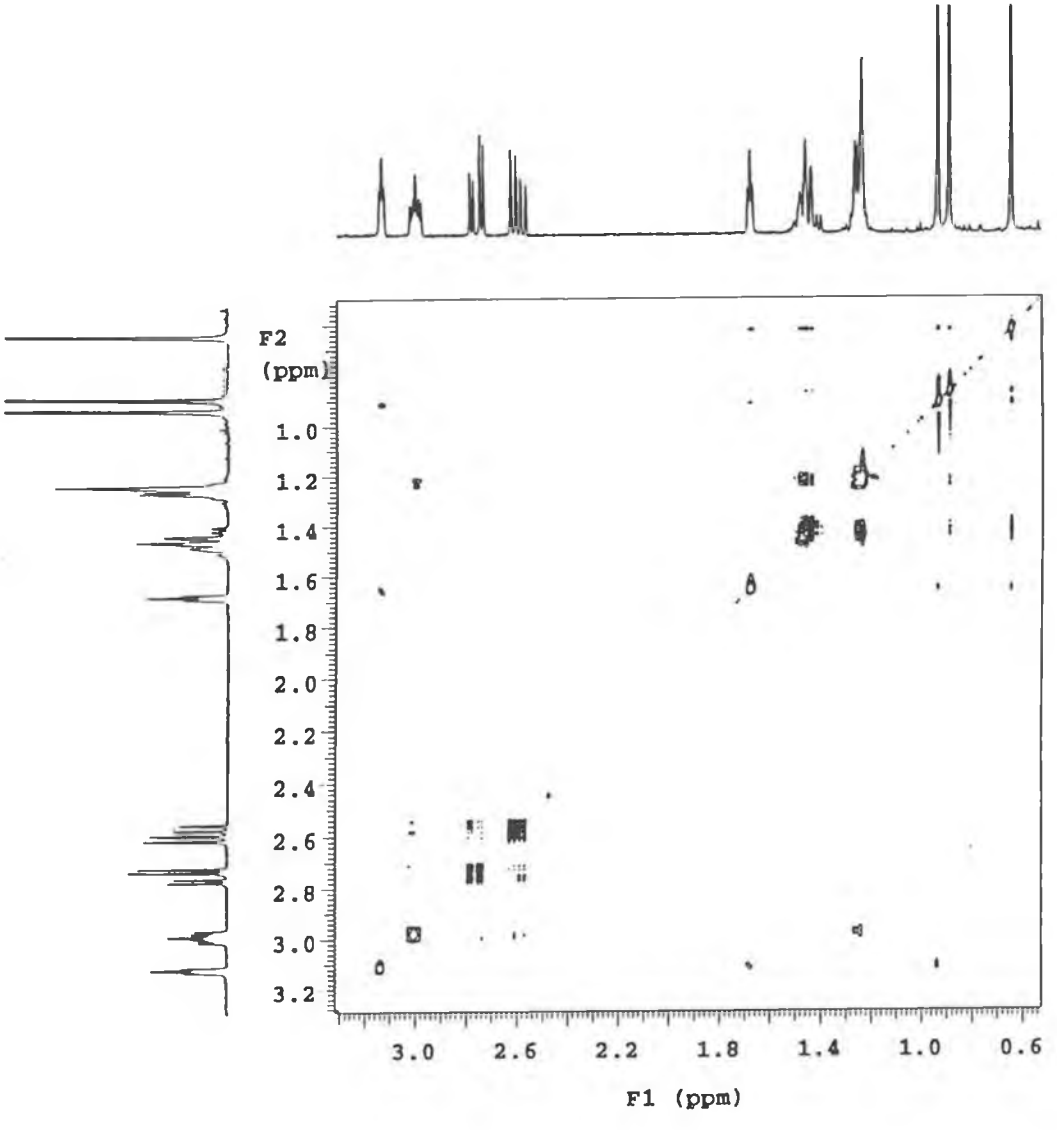
**44b**

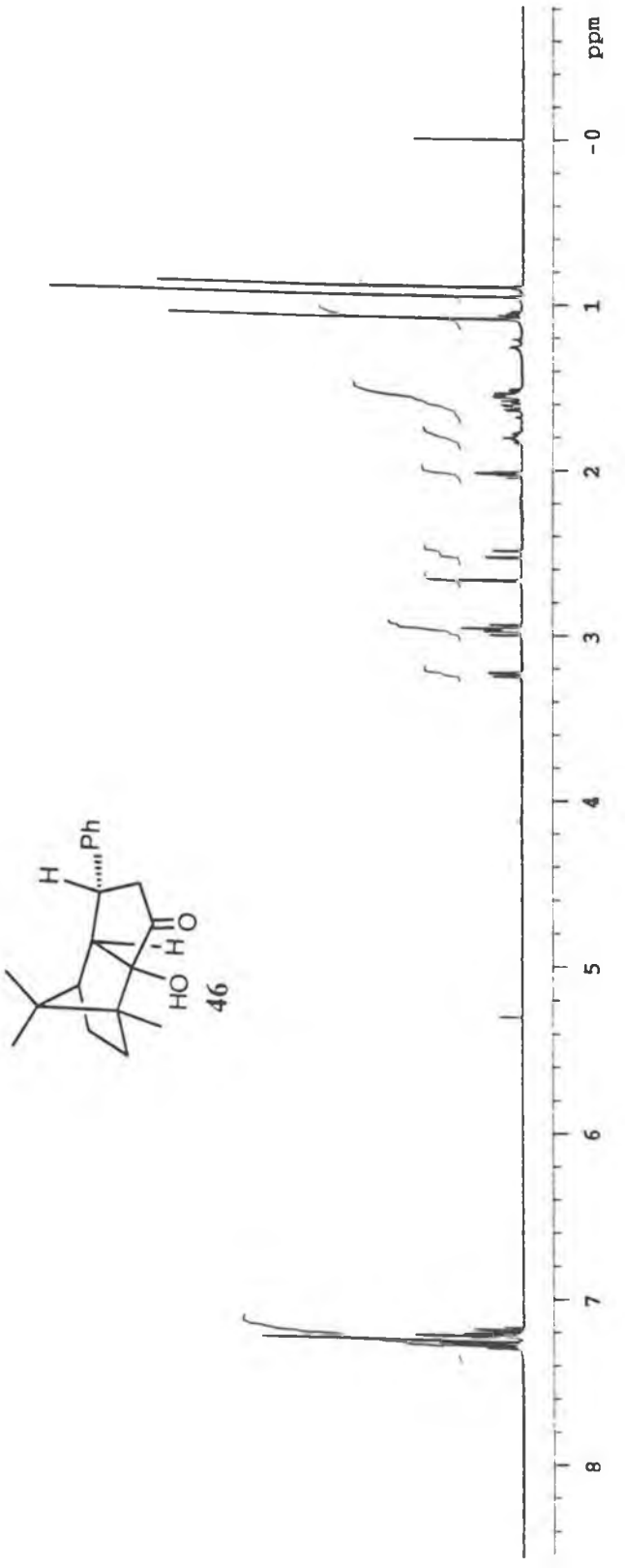

F2
(ppm)
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.4
3.0
2.6
2.2
1.8
1.4
1.0
F1 (ppm)

**NOESY of**

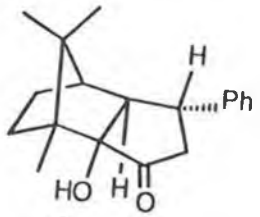

H
Br
Ph
O

**44b**

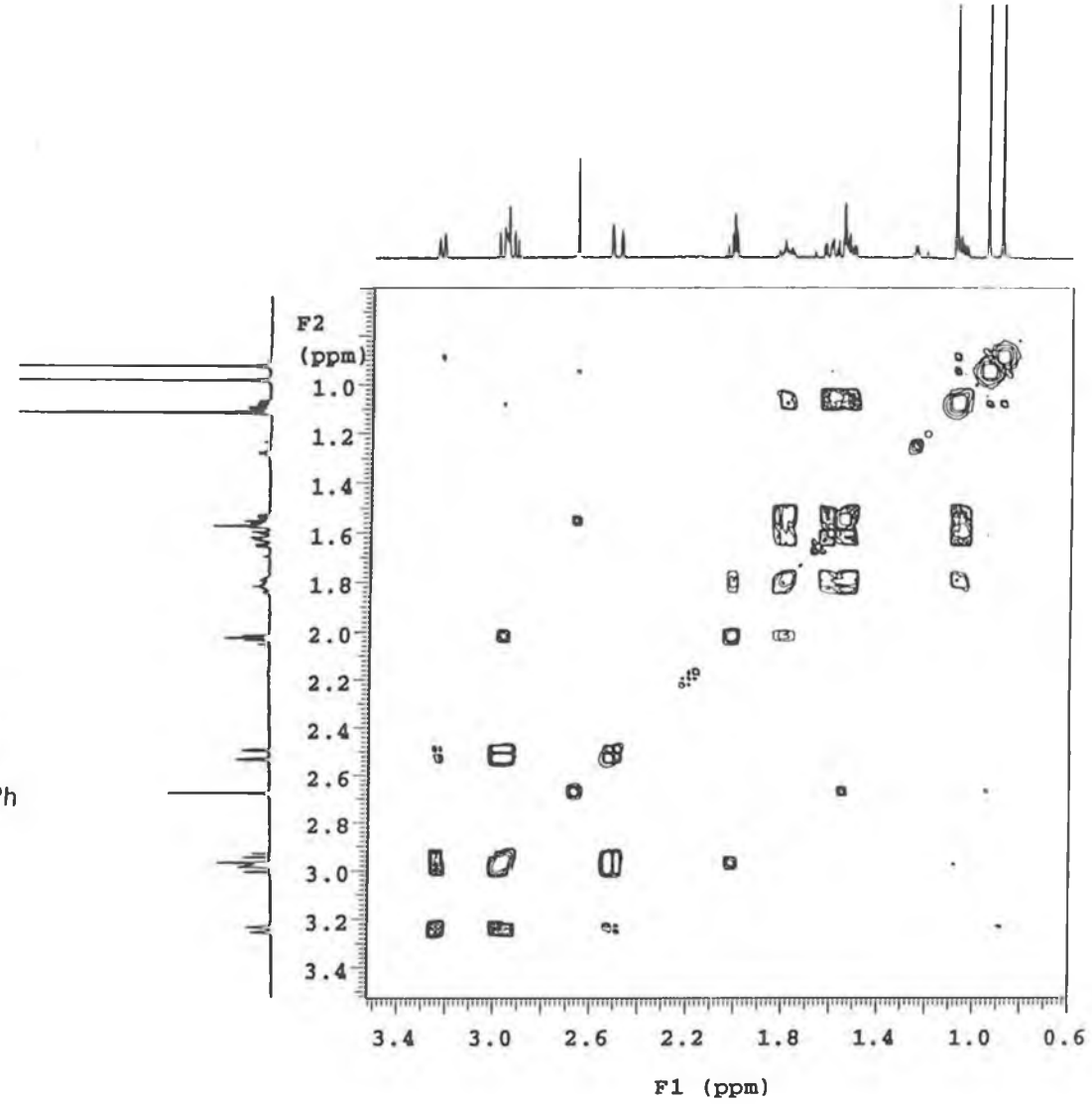

F2
(ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)


H
Ph
HO
H
O
46
8
7
6
5
4
3
2
1
-0
ppm

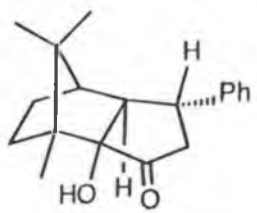
**COSY of**


H
Ph
HO
H
O

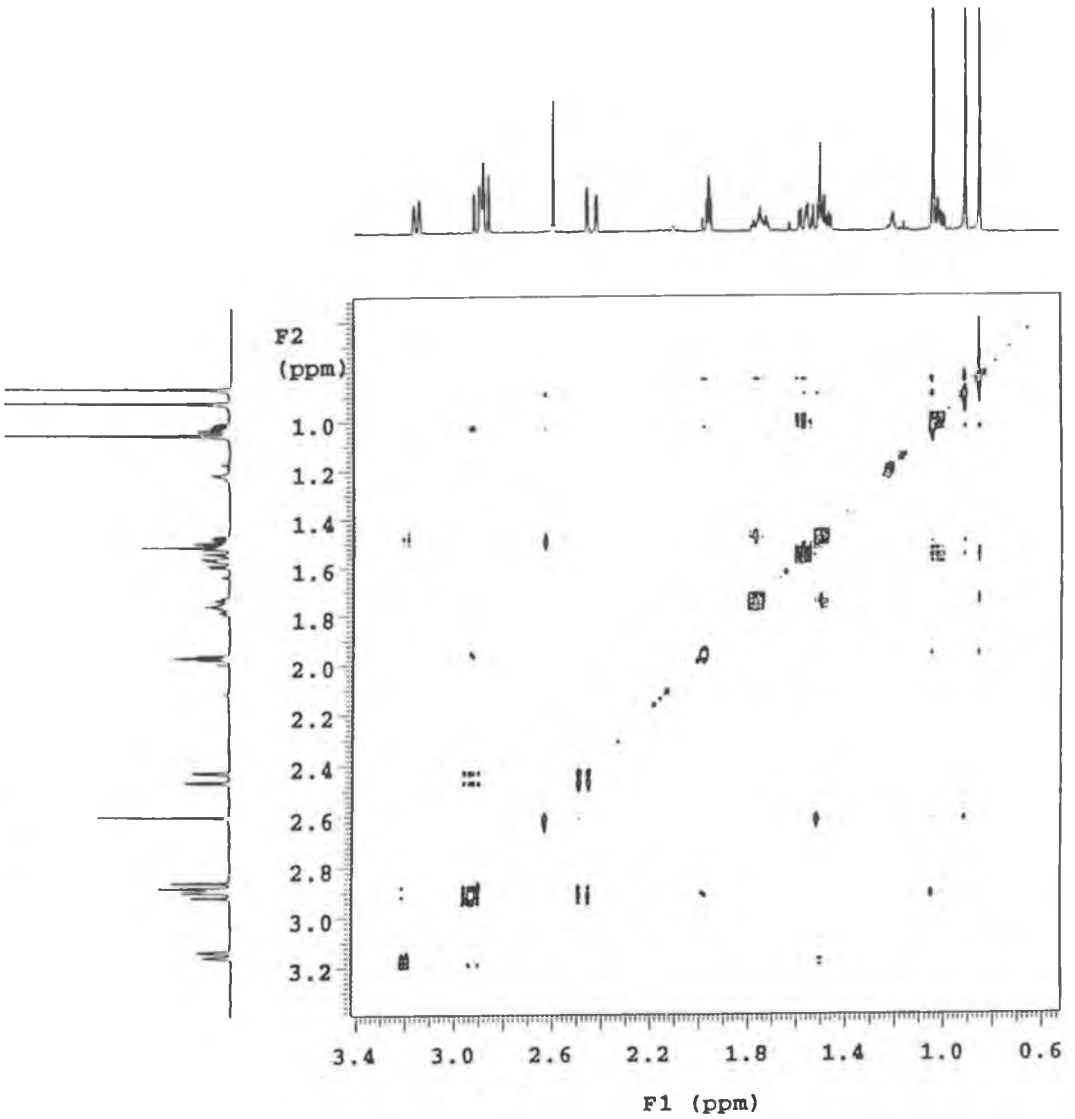
**46**


F2
(ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.4
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)

**NOESY of**


H
Ph
HO
H
O

**46**


F2
(ppm)
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.0
2.6
2.2
1.8
1.4
1.0
0.6
F1 (ppm)